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Forecasting the Essential Chemotherapy Needed for Treatment of Children with Acute Lymphoblastic Leukemia in Low- and Middle-Income Countries

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Abstract

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer, with contemporary therapy resulting in a 90% survival in high-income countries (HIC). However, an estimated 89% of the world's children live in low- and middle-income countries (LMIC) where survival is much lower. Lack of access to essential chemotherapy contributes significantly to the decreased survival rates for LMIC, and inaccurate forecasting of chemotherapy needed may lead to stockouts or oversupply. This chapter describes a simple forecasting system with population and patient-based multipliers for each drug used in the treatment of pediatric ALL, thus estimating the essential chemotherapy quantities needed for a single patient, facility, region, or country.

We described a forecasting model for estimating essential chemotherapy in the treatment of childhood ALL to multipliers. Multipliers were obtained from a reference population of 10 million children evenly distributed (2.5 million each) across four age cohorts at 5-year intervals (0-4, 5-9, 10-14, and 15-19 years). The forecasting model and multipliers were applied to 171 countries with age-specific population data available in the United Nations 2017 World Populations Prospects. Results from the forecasting model and multipliers were compared to determine differences for each country and for countries with extreme population distributions across the pediatric age range. The multipliers produced results no greater than 15% of those obtained using the forecasting model.

Multipliers allow healthcare providers, cancer centers, hospitals, countries, and drug manufacturers to accurately estimate the essential chemotherapy needs for a patient, facility, region, or country. This practical tool can be applied to other cancer diagnoses and treatment protocols.

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Forecasting the Essential Chemotherapy Needed for Treatment of Children with Acute Lymphoblastic Leukemia in Low- and Middle-Income Countries

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DEDICATION

I dedicate this dissertation to my family: my beloved wife, Yvette; my precious children, Jackson and Edison; my ever-loving parents, Richard and Shirley; and my supportive brother and sister, Alan and Monica. Without your love, support, and prayers, this would never have been possible.

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ABSTRACT

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer, with contemporary therapy resulting in a 90% survival in high-income countries (HIC). However, an estimated 89% of the world's children live in low- and middle-income countries (LMIC) where survival is much lower. Lack of access to essential chemotherapy contributes significantly to the decreased survival rates for LMIC, and inaccurate forecasting of chemotherapy needed may lead to stockouts or oversupply. This chapter describes a simple forecasting system with population and patient-based multipliers for each drug used in the treatment of pediatric ALL, thus estimating the essential chemotherapy quantities needed for a single patient, facility, region, or country.

We described a forecasting model for estimating essential chemotherapy in the treatment of childhood ALL to multipliers. Multipliers were obtained from a reference population of 10 million children evenly distributed (2.5 million each) across four age cohorts at 5-year intervals (0-4, 5-9, 10-14, and 15-19 years). The forecasting model and multipliers were applied to 171 countries with age-specific population data available in the United Nations 2017 World Populations Prospects. Results from the forecasting model and multipliers were compared to determine differences for each country and for countries with extreme population distributions across the pediatric age range. The multipliers produced results no greater than 15% of those obtained using the forecasting model.

Multipliers allow healthcare providers, cancer centers, hospitals, countries, and drug manufacturers to accurately estimate the essential chemotherapy needs for a patient, facility, region, or country. This practical tool can be applied to other cancer diagnoses and treatment protocols.

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LIST OF ABBREVIATIONS

ALL	Acute lymphoblastic leukemia
BFM	Berlin-Frankfurt-Munster regimen
CDC	Centers for Disease Control and Prevention
CRT	Cranial irradiation
CSR	Cancer Statistics Review
EMA	European Medicines Agency
EML	Essential medicines list
FDA	Food and Drug Administration
HIC	High-income countries
LMIC	Low- and middle-income countries
MG	Milligrams
MHRA	Medicines and Healthcare products Regulatory Agency
NCI	National Cancer Institute
NIH	National Institutes of Health
PODC	Pediatric Oncology in Developing Countries
SEER	Surveillance, Epidemiology, and End Results
UMIC	Upper-middle income countries
WHO	World Health Organization
6MP	Mercaptopurine

CHAPTER 1. INTRODUCTION

Background

Worldwide, each year approximately 429,000 children between the ages of 0 to 19 will develop cancer (Lam, Howard, Bouffet, & Pritchard-Jones, 2019). The 5-year survival rate for the 10% (or 42,900) of these children who live in high-income countries (HIC) exceeds 80% (Allemani et al., 2018; Bhakta, Martiniuk, Gupta, & Howard, 2013; Howard et al., 2008; Pritchard-Jones et al., 2013; Rodriguez-Galindo et al., 2015). In contrast, the 5-year survival rate for the remaining 90% (or 386,100) children who live in low- and middle-income countries (LMIC) is less than 30% in many places (Lam et al., 2019).

The most common cancer afflicting children worldwide is acute lymphoblastic leukemia (ALL), which accounts for 25% of all childhood cancers (Katz, Chia, Schoonen, & Kelsh, 2015). Fortunately, effective treatment is available, and in HIC, approximately 90% of children with ALL will survive with minimal long-term disability (Bhakta et al., 2013). In LMIC, however, cure rates for ALL are significantly lower than those in HIC (Allemani et al., 2015; Bhakta et al., 2013; Cooper & Brown, 2015; Jabbour, Pui, & Kantarjian, 2018; Jaime-Perez et al., 2016; Magrath et al., 2013; Pribnow, Ortiz, Baez, Mendieta, & Luna-Fineman, 2017; Redaniel et al., 2010).

Causes of preventable treatment failure in LMIC include lack of diagnosis, incorrect or delayed diagnosis, abandonment, treatment refusal, excessively high rates of toxic death, and relapse (Howard et al., 2017). Lack of access to essential chemotherapy is an important contributor to the disparate survival rates for LMIC that improve when issues impeding access are addressed (Denburg, Knaul, Atun, Frazier, & Barr, 2014; Lam et al., 2019; Moye-Holz, van Dijk, Reijneveld, & Hogerzeil, 2017; Simonyan et al., 2019). A key contributor to assuring access to required medication in LMIC lies in the accurate forecasting of demand for essential chemotherapy (Pisa & McCurdy, 2019). However, rarely is disease incidence used to calculate the demand for essential chemotherapy (Denburg et al., 2014). Data indicate that without utilizing disease incidence to inform inventory levels and buying patterns, minimal improvements in survival rates will occur (Denburg et al., 2014). The overall goal of the series of studies reported here was to develop a forecasting model and describe patient and population multipliers that estimate the annual essential chemotherapy required to treat ALL for a country based upon the estimated yearly incidence of ALL for that country.

Study Aims

The aim of the first study was to develop a model to forecast the required mercaptopurine (one of several essential chemotherapeutics needed to treat ALL) to treat every child with ALL in an LMIC annually, using the Philippines as an example. Readily available data sources were utilized to develop the forecasting model. Surveillance, Epidemiology, and End Results data (SEER) were utilized to estimate the incidence rate of ALL. The SEER Cancer Statistics Review 1975 – 2016 was chosen for 3 reasons. First, ALL incidence peaks in children at 2 to 3 years of

age, but the incidence does vary by age, each year, and SEER provides yearly incidence rates, in 1-year intervals, for children up to the age of 19 (National Institutes of Health, 2010). Second, SEER data were analyzed and refreshed yearly if needed. Third, SEER data were believed to be appropriate for LMIC since variation in international incidence of ALL is thought to be minimal (Katz et al., 2015; Lam et al., 2019). The study population reflected the 2015 Philippines Census Data that provided male and female children and adolescents in 1-year intervals up to the age of 19. For body surface area, the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) growth charts provided length or height and weight for males and females to calculate body surface area at 1-year intervals for children up to 19 years of age. Both are based on rigorous study designs for growth assessment, and these standards and measurements are consistently reviewed. Risk-group categorization was needed since drug utilization and dosing was based upon low-, medium-, and high-risk categorization. The Berlin-Frankfurt-Munster (BFM) protocol studied from 1981 to 2000, with nearly 7,000 children with ALL, was used to estimate the percentages of patients expected to fall into each risk stratum. The International Society of Pediatric Oncology (SIOP) ALL Adapted Regimens, adapted for LMIC, was used for the forecasting model. The SIOP ALL Adapted Regimens were developed with consideration of the resources of cancer centers within LMIC (Hunger, Sung, & Howard, 2009).

The aim of the second study was to expand the forecasting model to include the quantity of every essential chemotherapy needed to treat each child and adolescent diagnosed with ALL. The forecasting model was applied to three levels of emerging countries: Tanzania for low-income; Honduras for lower-middle-income; and Venezuela for upper-middle-income (World Bank, 2018). Ensuring timely, accurate, and consistent population data across the three countries' census processes could not be achieved. Therefore, the United Nations (UN) World Population Prospects was utilized to provide male and female children and adolescent data in 1-year intervals up to the age of 19; these population projections utilized all available data on population size, including 1,700 censuses (United Nations, 2019). It also included mortality, fertility, and international migration projections for all regions and countries which comprise the population of the world. The UN World Population projections are refreshed every year.

The aim of the third study was to describe multipliers that achieve results similar to those of the forecasting model but with greatly simplified inputs that enable rapid estimation of the essential chemotherapy needed to treat ALL for any individual patient, cancer treatment facility, country, or region. The patient multiplier was a given number that can be multiplied by any number of children 0-19 years of age with ALL to estimate their needed essential chemotherapy for treatment. The population multiplier was a given number that could be multiplied by a population of children 0-19 years of age to estimate the needed essential chemotherapy for the projected incidence of pediatric ALL. The forecasting multipliers were developed by a hypothetical population of 10,000,000 children evenly distributed (2.5 million each) across four 5-year interval age cohorts (0-4, 5-9, 10-14, and 15-19 years) calculated by the forecasting model projection. Patient multipliers were calculated by dividing the total chemotherapy dosage required to treat the projected ALL incidence by population (354). Population multipliers were calculated by dividing the total milligrams (mg) of the given chemotherapy required to treat the population by the population (10,000,000).

CHAPTER 2. FORECASTING THE NEED FOR ESSENTIAL CHEMOTHERAPY FOR CHILDREN WITH CANCER IN LOW- AND MIDDLE-INCOME COUNTRIES: MERCAPTOPURINE IN THE PHILIPPINES

Introduction

Event-free survival for children and adolescents diagnosed with acute lymphoblastic leukemia (ALL) exceeds 85% in high-income countries (HIC); however, event-free survival is much lower in LMIC (Allemani et al., 2015; Bhakta et al., 2013; Jabbour et al., 2018; Jeha et al., 2019; Magrath et al., 2013; Pribnow et al., 2017; Redaniel et al., 2010). Treatment failure in LMIC is multifactorial and may include lack of diagnosis, delayed or incorrect diagnosis, refusal, abandonment, toxic death, and preventable relapse (Howard et al., 2017). One cause of preventable relapse is lack of access to essential chemotherapy, which often occurs as a result of systemic factors including national or regional drug shortages and stock-outs (Ruff, Al-Sukhun, Blanchard, & Shulman, 2016). Mercaptopurine (6MP) has been an essential drug in the treatment of ALL for over 50 years and is considered an essential cancer medication by the World Health Organization (WHO) (Barr & Robertson, 2016; Gaynon, 2017; Singh, Bhatia, Khera, & Trehan, 2017; Smid, Karas-Kuzelicki, Jazbec, & Mlinaric-Rascan, 2016).

The International Pediatric Oncology Society (SIOP) Pediatric Oncology in Developing Countries (PODC) Essential Medicines Working Group has identified 6MP access as a significant challenge for LMIC, especially after the 2017 prolonged national shortage in the Philippines (Mehta, Wiernikowski, Petrilli, Barr, & Working Group on Essential Medicines of the Pediatric Oncology in Developing Countries committee of SIOP, 2013). Drug shortages are multifactorial, with production being one common factor resulting from a drug company no longer producing the drug or manufacturing facilities that may close due to unforeseen circumstances. Complex regulatory procedures require substantial time and funding for drug manufacturing replacements, and mechanisms to accrue emergency supplies can be difficult to initiate (Allemani et al., 2015). Compounding these difficulties, low-standing inventories and complex in-country supply chains make national or sub-national shortages likely during the transition to a new supplier. Forecasting the maximum quantity of monthly chemotherapy requirements at the national level would allow the country to maintain several months of inventory. This is particularly true for inexpensive generic drugs like 6MP which have a long shelf-life and no comparable substitutes.

Herein, we describe a model that utilizes the age distribution of children in the Philippines, age-standardized incidence of childhood ALL, and mean body surface area by age based on height and weight tables to predict the quantity of 6MP needed annually to treat every child and adolescent diagnosed with ALL in the Philippines. Such forecasting assures adequate monthly supplies and inventory at the national level to withstand shortages due to the potential loss of a supplier and other factors. This model is practical and can be applied regardless of the cancer type, treatment protocol, or drugs of interest.

Methods

Acute Lymphoblastic Leukemia Incidence Estimates

Philippines 2015 census data released Friday, June 30, 2017, were used to determine the male and female population in one-year intervals for children and adolescents through 19 years of age (Philippine Statistics Authority, 2017). The National Institutes of Health (NIH); National Cancer Institute (NCI); and Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review (CSR) 1975-2010 data were used to determine the incidence of ALL in one-year intervals by multiplying the CSR incidence rate per 100,000 per year by the population of children of that age from the Philippines census data (National Institutes of Health, 2010).

Body Surface Area Estimates

The WHO and CDC growth charts provided length/height and weight for males and females to calculate body surface area at 1-year intervals for patients 0-19 years of age (Centers for Disease Control and Prevention, 2010). WHO length and weight charts were used for males and females from age 0-24 months of age, while the CDC growth charts were used for males and females 3-19 years of age. WHO length and growth charts were used for infants and toddlers 0-24 months, as these growth charts provide normative standards for breastfed children and are more consistent with the physiological description of growth in infancy. WHO growth charts do not provide data for children over 5 years old; however, the methods for CDC and WHO growth charts are similar for children 2-5 years of age and both are based on rigorous study designs for growth assessment (Centers for Disease Control and Prevention, 2010).

Protocols for Acute Lymphoblastic Leukemia

The SIOP Adapted ALL Regimens for use in LMIC is utilized in the Philippines and likewise was used as a model protocol in our forecasting model (Hunger et al., 2009). The SIOP Adapted ALL Regimens includes 3 risk strata and 3 types of oncology centers, which have been described elsewhere to identify the optimal regimen for each patient based upon leukemia risk features and resources available at the treatment center (Howard et al., 2017). Centers were defined by supportive care resources, with setting 1 centers having limited supportive care; therefore, the use of intense chemotherapy regimens is associated with an unacceptably high rate of toxic death; setting 2 centers have intermediate supportive care; and setting 3 centers are comparable to centers in HIC. The initial forecast calculation was based on setting 2 regimens, which are comparable to most centers in the Philippines. The estimated 6MP quantity was also calculated for setting 1 and 3 centers to determine if this would significantly change the amount of 6MP needed. The detailed 6MP quantity according to center is detailed in **Tables 2-1** to **2-4**.

The SIOP Adapted ALL Regimens stratify risk based on age, white blood cell count, central nervous system status at diagnosis, and early response to treatment. The three risk categories are lower risk, higher risk, and very high risk.

Table 2-1. Estimated numbers of children who develop acute lymphoblastic leukemia in the Philippines

	Children by year of age			Cases of childhood ALL			
Age	Both sexes	Female	Male	ALL incidence*	Both sexes	Female	Male
0	2,075,441	1,002,348	1,073,093	2	42	20	21
1	2,090,348	1,011,207	1,079,141	4.6	96	47	50
2	2,190,994	1,059,470	1,131,524	9.8	215	104	111
3	2,234,812	1,079,682	1,155,130	9.5	212	103	110
4	2,224,403	1,074,395	1,150,008	7.6	169	82	87
5	2,180,700	1,053,790	1,126,910	4.6	100	48	52
6	2,172,796	1,052,777	1,120,019	4.4	96	46	49
7	2,236,650	1,080,921	1,155,729	3.2	72	35	37
8	2,139,569	1,035,343	1,104,226	2.6	56	27	29
9	2,109,160	1,021,322	1,087,838	2.7	57	28	29
10	2,191,716	1,055,585	1,136,131	2.4	53	25	27
11	2,084,417	1,011,595	1,072,822	2.3	48	23	25
12	2,092,242	1,018,281	1,073,961	1.9	40	19	20
13	2,026,422	986,865	1,039,557	2.1	43	21	22
14	2,085,615	1,010,573	1,075,042	2.2	46	22	24
15	2,198,355	1,062,568	1,135,787	2	44	21	23
16	1,956,206	955,414	1,000,792	2.2	43	21	22
17	2,020,544	986,426	1,034,118	1.6	32	16	17
18	2,015,993	996,061	1,019,932	1.7	34	17	17
19	1,929,214	955,586	973,628	1.4	27	13	14
Total	42,255,597	20,510,209	21,745,388		1,523	738	785

Notes: ALL – Acute lymphoblastic leukemia. Population data retrieved from Philippine Statistics Authority. (2017). Philippine Population Surpassed the 100 Million Mark (Results from the 2015 Census of Population). Retrieved from https://www.psa.gov.ph/content/philippine-population-surpassed-100-million-mark-results-2015-census-population. ALL rate data retrieved National Institutes of Health. (2010). National Institutes of Health National Cancer Institute Surveillance, Epidemiology, and End Results. Retrieved from https://seer.cancer.gov/archive/csr/1975_2010/browse_csr.php?sectionSEL=28&pageSEL=sect_28_table.13.html.

*This number represents ALL incidence per million children per year.

Table 2-2. Mercaptopurine needed in the Philippines each year, assuming that all centers use setting 2 regimens

Age	Total mg of 6MP	Approximate 50mg tablets	Approximate bottles of 30 tablets/50mg
0	913,345	18,267	609
1	2,477,153	49,543	1,651
2	6,724,258	134,485	4,483
3	7,560,640	151,213	5,040
4	6,651,099	133,022	4,434
5	4,341,345	86,827	2,894
6	4,526,172	90,523	3,017
7	3,686,621	73,732	2,458
8	3,105,628	62,113	2,070
9	3,439,300	68,786	2,293
10	3,435,135	68,703	2,290
11	3,389,262	67,785	2,260
12	3,043,988	60,880	2,029
13	3,512,450	70,249	2,342
14	4,039,293	80,786	2,693
15	4,070,295	81,406	2,714
16	4,127,649	82,553	2,752
17	3,176,756	63,535	2,118
18	3,422,067	68,441	2,281
19	2,731,751	54,635	1,821
Total	78,374,206	1,567,484	52,249

Notes: 6MP – Mercaptopurine; mg – milligrams; m2 – meters squared; ml – milliliters. Setting 2 centers typically have intermediate supportive care and an approximate 5-year event-free survival of 50–65%. Population data retrieved from Philippine Statistics Authority. (2017). Philippine Population Surpassed the 100 Million Mark (Results from the 2015 Census of Population). Retrieved from https://www.psa.gov.ph/content/philippine-population-surpassed-100-million-mark-results-2015-census-population. Length/height and weight data retrieved from the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) growth charts at https://www.cdc.gov/growthcharts/who_charts.htm#The%20WHO%20Growth%20Charts on 08-19-2019. Risk group percentages based upon ALL-BFM study group from 1981 to 2000. Dosage based upon International Society of Pediatric Oncology (SIOP) Adapted Regimen for Acute Lymphoblastic Leukemia (ALL) - Step 2 Center.

Table 2-3. Mercaptopurine needed at 100% Setting 1 centers

Age	Total mg of 6MP	Approximate 50mg tablets	Approximate bottles of 30 tablets/50mg
0	953,351	19,067	636
1	2,585,291	51,706	1,724
2	7,018,212	140,364	4,679
3	7,892,032	157,841	5,261
4	6,942,796	138,856	4,629
5	4,531,556	90,631	3,021
6	4,723,311	94,466	3,149
7	3,848,185	76,964	2,565
8	3,241,362	64,827	2,161
9	3,589,422	71,788	2,393
10	3,586,991	71,740	2,391
11	3,536,509	70,730	2,358
12	3,175,360	63,507	2,117
13	3,663,739	73,275	2,442
14	4,215,123	84,302	2,810
15	4,248,208	84,964	2,832
16	4,303,719	86,074	2,869
17	3,312,306	66,246	2,208
18	3,564,121	71,282	2,376
19	2,844,481	56,890	1,896
Total	81,776,075	1,635,522	54,517

Notes: 6MP – mercaptopurine; mg – milligrams; m2 – meters squared; ml– milliliters. Setting 1 Centers indicate limited supportive care and less than a 50% event-free survival (EFS) rate. Population data retrieved from Philippine Statistics Authority. (2017). Philippine Population Surpassed the 100 Million Mark (Results from the 2015 Census of Population). Retrieved from https://www.psa.gov.ph/content/philippine-population-surpassed-100-million-mark-results-2015-census-population. Length/height and weight data retrieved from the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) growth charts at https://www.cdc.gov/growthcharts/who_charts.htm#The%20WHO%20Growth%20Charts on 08-19-2019. Risk group percentages based upon ALL-BFM study group from 1981 to 2000. Dosage based upon International Society of Pediatric Oncology (SIOP) Adapted Regimen for Acute Lymphoblastic Leukemia (ALL) - Step 1 Center.

Table 2-4. Mercaptopurine needed to cover 100% of children in the Philippines using the Setting 3 regimens

Age	Total mg of 6MP for Step 3	Approximate 50mg tablets	Approximate bottles of 30 tablets/50mg
0	884,137.40	17,683	29,471
1	2,467,314.11	49,346	82,244
2	6,698,085.79	133,962	223,270
3	7,532,152.97	150,643	251,072
4	6,626,182.28	132,524	220,873
5	4,324,975.93	86,500	144,166
6	4,508,318.88	90,166	150,277
7	3,672,857.90	73,457	122,429
8	3,093,823.68	61,876	103,127
9	3,426,150.95	68,523	114,205
10	3,423,459.32	68,469	114,115
11	3,375,936.07	67,519	112,531
12	3,031,400.50	60,628	101,047
13	3,497,557.47	69,951	116,585
14	4,023,137.52	80,463	134,105
15	4,054,130.37	81,083	135,138
16	4,107,786.70	82,156	136,926
17	3,161,313.08	63,226	105,377
18	3,402,487.65	68,050	113,416
19	2,715,607.92	54,312	90,520
Total	78,026,816.49	1,560,536	52,018

Notes: 6MP – mercaptopurine; mg – milligrams; m2 – meters squared; ml, milliliters. Setting 1 Centers indicate limited supportive care and less than a 50% event-free survival (EFS) rate. Population data retrieved from Philippine Statistics Authority. (2017). Philippine Population Surpassed the 100 Million Mark (Results from the 2015 Census of Population). Retrieved from https://www.psa.gov.ph/content/philippine-population-surpassed-100-million-mark-results-2015-census-population. Length/height and weight data retrieved from the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) growth charts at https://www.cdc.gov/growthcharts/who_charts.htm#The%20WHO%20Growth%20Charts on 08-19-2019. Risk group percentages based upon ALL-BFM study group from 1981 to 2000. Dosage based upon International Society of Pediatric Oncology (SIOP) Adapted Regimen for Acute Lymphoblastic Leukemia (ALL) - Step 3 Center.

No published population-based studies were available to assign risk groups to Filipino children using data from the Philippines at the national level, so data from five consecutive ALL trials with the Berlin-Frankfurt-Munster (BFM) protocol from 1981 to 2000 were used to estimate the percentages of patients who would be expected to fall into each risk stratum (Moricke et al., 2010). The BFM protocols from 1981 to 2000 included 6,607 children, of whom 2,435 (37%) were low risk, 3,479 (53%) were medium risk, and 693 (10%) were high risk. These percentages were used for the risk group estimates in the prediction model. Although the risk nomenclature for the SIOP Adapted ALL and BFM protocols are different, the criteria for the risk stratifications are similar and interchangeable.

Results

The estimated annual incidence of ALL in the Philippines for children 0-19 years of age was 1,523 **(Table 2-1)**. Assuming that all centers treated according to the SIOP Adapted ALL Regimens for setting 2, the estimated maximum quantity of 6MP for children 0-19 years of age was 1,567,484 50 mg tablets per year, equating to approximately 130,000 50mg tablets per month **(Table 2-2)**. The estimated maximum 6MP quantities for children and adolescents diagnosed with ALL in the Philippines is depicted for the 3 setting types in **Tables 2-2** to **2-4**. Estimated leukemia risk groups by age cohort and sex are depicted in **Table 2-5**, with 564 (37%) at lower risk, 807 (53%) at higher risk, and 152 (10%) at very high risk.

Sensitivity Analysis for Incidence

Incidence estimated from age-standardized rates may not apply to all countries, with incidence rates varying among countries with high-quality, population-based cancer registries. For example, the CDC estimated the incidence of ALL as 34.0 cases per 1 million children at 0-19 years of age, which would predict 1,437 children per year with ALL in the Philippines or 5.6% less than our estimate of 1,523 (Siegel et al., 2017). The NCI estimated the incidence of ALL as 41 cases per million children who are 0-14 years of age and 17 cases per million children 15-19 years of age, which would predict 1,490 children per year with ALL in the Philippines or 2.2% less than our estimates (National Cancer Institute, 2018). Though variations in incidence have been reported as minimal across countries, we proposed adding 10% to the monthly estimated need since prevention of shortages is paramount to maximize the cure rate and reduce morbidity, mortality, and costs associated with treating relapsed ALL (Katz et al., 2015).

Sensitivity Analysis for Height, Weight, and Body Surface Area

Chemotherapy predictions utilizing standardized, non-country specific growth charts may introduce errors in the estimated need. The WHO and CDC growth curves follow well-defined standards and references, but values for children in each country inevitably differ among regions or ethnic groups even within the same country, having variability in weights and heights at each age. Therefore, WHO and CDC growth curves for Filipino children may overestimate chemotherapy needs (de Onis, Blossner, & Borghi, 2010; Poskitt, 2014). For example, the WHO

Table 2-5. Demographic information about children with acute lymphoblastic leukemia in the Philippines

	Childhood ALL cases			Length/height		Weight		Surface area		Risk group		
Age	ALL cases	Female	Male	Female	Male	Female	Male	Female	Male	37% lower	53% higher	10% Very high
0	42	20	21	65.73	67.62	7.30	7.93	0.37	0.39	15	22	4
1	96	47	50	74.02	75.75	8.95	9.65	0.43	0.45	36	51	10
2	215	104	111	86.42	87.82	11.48	12.15	0.52	0.54	79	114	21
3	212	103	110	93.92	94.96	13.87	14.33	0.60	0.61	79	113	21
4	169	82	87	100.75	102.22	15.79	16.23	0.66	0.68	63	90	17
5	100	48	52	107.66	108.90	17.93	18.39	0.73	0.75	37	53	10
6	96	46	49	114.71	115.39	20.24	20.68	0.80	0.81	35	51	10
7	72	35	37	121.49	121.77	22.76	23.07	0.88	0.88	26	38	7
8	56	27	29	127.59	127.88	25.63	25.64	0.95	0.95	21	29	6
9	57	28	29	132.92	133.51	28.99	28.55	1.03	1.03	21	30	6
10	53	25	27	137.99	138.62	32.89	31.94	1.12	1.11	19	28	5
11	48	23	25	143.98	143.52	37.21	35.89	1.22	1.20	18	25	5
12	40	19	20	151.19	149.05	41.65	40.47	1.32	1.29	15	21	4
13	43	21	22	157.15	156.09	45.82	45.59	1.41	1.41	16	23	4
14	46	22	24	160.39	163.84	49.36	51.00	1.48	1.52	17	24	5
15	44	21	23	161.86	169.94	52.04	56.28	1.53	1.63	16	23	4
16	43	21	22	162.55	173.51	53.88	60.92	1.56	1.71	16	23	4
17	32	16	17	162.91	175.29	55.14	64.57	1.58	1.77	12	17	3
18	34	17	17	163.12	176.16	56.19	67.20	1.60	1.81	13	18	3
19	27	13	14	163.25	176.60	57.30	69.12	1.61	1.84	10	14	3
Total	1,523	738	785							564	807	152

Notes: Length/Height, Weight data retrieved from the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) growth charts https://www.cdc.gov/growthcharts/who_charts.htm#The%20WHO%20Growth%20Charts. Surface area calculated via Mosteller formula. Risk group percentages based upon ALL-BFM study group from 1981 to 2000.

reported that 12.8% of Filipino children are overweight compared to 41.8% in the US (World Health Organization, 2018); greater obesity among children in the US and more growth-stunting in the Philippines could lead to underestimation of chemotherapy needed for children in the US and overestimation of chemotherapy needed for children in the Philippines (World Health Organization, 2018). Where age-specific obesity rates are known, the model could be refined, but we favor the use of individual patient data to create exact forecasts by patient, center, region, and country rather than attempts to increase the precision of the forecast beyond what is necessary to prevent stock-outs and shortages. However, doses of 6MP and other chemotherapy agents are calculated by body surface area rather than weight, and the increase in dose varies with the square root of the increase in weight. Therefore, a child weighing 100% more than the mean weight for a given age would require only 41% more chemotherapy.

Discussion

Summary of Findings

Forecasting the maximum quantity of 6MP is feasible using existing public data sources. Such forecasting is the first step in assuring an uninterrupted supply of essential chemotherapy, and this method may be applied to other chemotherapy agents. Estimation of the maximum quantity needed may serve as the foundation for other chemotherapy estimates. The actual requirement could be calculated if misdiagnosis, refusal, abandonment, and death could be calculated. Other considerations should include the feasibility of preparing liquid formulations and the stability of formulations as well as the need to cut pills according to prescribed dose. Dosing variations may require cutting 6MP tablets into fourths (e.g., for a dose of 62.5 mg per day, which requires 1¼ tablets). However, pending more nuanced estimates, procurement based on the upper bound could ensure a fixed minimal inventory sufficient to supply the country with the drug (or hospital or individual) should a replacement in supplier be needed.

Strengths of Study

The primary strength of this study was the projection of maximum chemotherapy needed using publicly available statistics. Census data in the Philippines are of high quality and available in yearly intervals. The WHO and CDC growth charts could be used for any country, and SEER incidence rates do not differ dramatically from incidence rates in other countries (Allemani et al., 2015; Centers for Disease Control and Prevention, 2010). SIOP Adapted ALL Regimens are appropriate for all countries, and the various regimens include approximately the same amount of 6MP (but not other agents), such that even if the regimens used at each cancer center within a country are not known, the 6MP forecast is accurate (Hunger et al., 2009).

Weaknesses of Study

Using surrogate measures of ALL incidence, non-Filipino growth curves to calculate doses needed at each age, and imputed percentages of each ALL risk group may introduce errors

in estimated chemotherapy needs. Furthermore, the census population at each age was based on 2015 data, and the number of patients at each age group may have been higher or lower according to the change in population from the time of the census used for the forecast. The forecast model did not use in-country ALL incidence rate, risk stratification, height and weight, and actual patient adherence or treatment regimen. Patient-level data addressed all of these weaknesses and directly measured incidence and relied on measurement of patients' actual height and weight rather than estimates from population curves. Patient-level data also considered the treatment regimen used and critical outcomes that would affect the amount of 6MP needed. Information systems are also available at no cost (e.g., http://www.amplifyinghealth.org/), facilitating direct measurements and calculation of a patient's forecasted individualized need.

Future Directions Regarding Information Systems

An information system that collects patient-level data could simultaneously create accurate forecasts and document when access to essential chemotherapy is limited, serving as a large-scale early warning system for drug shortages. Patient-level data allow forecasting at the individual level to ensure an adequate supply for the specific patient, aggregated at the center level, according to regional and national forecasts for bulk purchasing and procurement of adequate supplies. An information system that captures refusal, toxic death, abandonment, and relapse may allow adjustments to the forecasting model to more accurately reflect actual utilization of essential chemotherapy. A forecast based on patient-level information can inform governmental agencies charged with provision of a continuous supply of essential medicines and may prevent future shortages by ensuring that a 6-month supply is always on hand. The information system can be linked to health insurance coverage to ensure that it corresponds to patients' needs and allows nuanced application of national funding mechanisms like the PhilHealth Z-package designed for coverage of severe conditions (PhilHealth, 2018).

More work is needed, but ALL is a curable cancer at a relatively low cost. Assuring an uninterrupted supply of essential chemotherapy is feasible. Age-standardized incidence rates, growth curves, imputed risk stratification, and census data enable forecasting by cancer type and chemotherapy agent at any level of society (individual, hospital, and nation). Such models can inform healthcare policy and eliminate needless deaths from curable cancers that would otherwise result because of the unavailability of low-cost, essential drugs and resources.

Conclusion

Forecasting the maximum national needs for chemotherapeutic agents is feasible using existing public data sources. However, in-country patient-level information that includes refusal, abandonment, toxic death, and relapse is needed to estimate needs more precisely. Our results showed that using such models could help to effectively treat curable cancers worldwide.

CHAPTER 3. FORECASTING THE ESSENTIAL CHEMOTHERAPY NEEDED FOR TREATMENT OF CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA IN LOW- AND MIDDLE-INCOME COUNTRIES: TANZANIA, HONDURAS, AND VENEZUELA

Introduction

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer, with contemporary therapy resulting in 90% survival in high-income countries (HIC) (Cooper & Brown, 2015; Essig et al., 2014; Jaime-Perez et al., 2016; Jeha et al., 2019). An estimated 87% of the world's children live in low- and middle-income countries (LMIC) where ALL cure can be elusive (Allemani et al., 2015; Bhakta et al., 2013; Cooper & Brown, 2015; Jabbour et al., 2018; Jaime-Perez et al., 2016; Magrath et al., 2013; Pribnow et al., 2017; Redaniel et al., 2010).

Treatment failures in LMIC have been identified as incorrect or delayed diagnosis, abandonment, treatment refusal, and preventable relapse (Howard et al., 2017). Preventable relapse occurs when a child lacks access to essential chemotherapy resulting from systemic factors including stock-outs and national or regional drug shortages (Ruff et al., 2016). Other contributing factors may include insufficient medical infrastructure and family resources. Insufficient medical infrastructure contributes to inadequate access to tests necessary for diagnosis and patient risk stratification (Jeha et al., 2019; Ruff et al., 2016). Utilization of suboptimal chemotherapy treatment regimens, insufficient access to cancer treatment centers, lack of oncological healthcare providers, and lack of supportive care are also problematic (Hunger et al., 2009; Jeha et al., 2019; Ruff et al., 2016). Insufficient family resources may result in lack of access to care due to barriers of transportation, costs of food and lodging near the treatment center, and costs for medical services (Howard et al., 2017; Ruff et al., 2016).

Through the SIOP ALL Adapted Regimens, efforts have been implemented to address the essential chemotherapy needs for treatment of ALL in LMIC (Hunger et al., 2009). The SIOP ALL Adapted Regimens were developed with consideration of the cancer center and supportive care infrastructure within LMIC. The protocol describes three levels of care, with four treatment regimens comprised of 6 to 9 medications, all of which the WHO and SIOP Pediatric Oncology in Developing Countries (PODC) Essential Medicines Working Group consider essential chemotherapy (Mehta et al., 2013; World Health Organization, 2019). Within the SIOP ALL Adapted Regimens, all chemotherapy is generic, available from multiple distributors, and relatively affordable. Although protocols are center-specific and the essential chemotherapy is generic and affordable, achieving higher ALL cure rates in LMIC is not possible without an adequate supply of essential chemotherapy.

Drug shortages are multifactorial and occur in both HIC and LMIC (Iyengar, Hedman, Forte, & Hill, 2016). Sixty-six percent of drug shortages are directly related to manufacturing and have become more prevalent in recent years, especially for inexpensive generic drugs (World Heath Organization, 2016). Less often (14%), drug shortages are related to discontinuation of the product, raw material shortage (8%), increased demand (6%), and loss of a manufacturing site (4%) (Fisher, Wicks, & Babar, 2016; Gray & Manasse, 2012; Iyengar et al.,

2016; United States Food and Drug Administration, 2013; World Heath Organization, 2016). A reliable estimate of the annual essential chemotherapy need would enable a country to strategically manage purchasing and inventory to mitigate a drug shortage. This strategical buying would allow any country the ability to have essential chemotherapy on-hand within a predicted time frame. Should supply problems arise, this predictive buying plan would allow the patient to continue ALL treatment while health care officials resolve upstream supply issues. This chapter describes a forecasting model that utilizes three readily available data sources to predict the annual incidence of pediatric ALL and the quantity of essential chemotherapy needed to treat each child and adolescent diagnosed with ALL. Three countries—Tanzania, Honduras, Venezuela—serve as examples of low-income, lower middle-income, and upper middle-income countries for this forecasting model (Centers for Disease Control and Prevention, 2010; National Institutes of Health, 2010; United Nations, 2019; World Bank, 2018).

Methods

Protocols for Acute Lymphoblastic Leukemia

The SIOP Adapted ALL protocol regimen adapted for LMIC was used for the forecasting model (Hunger et al., 2009). This protocol stratifies risk by age, white blood cell count, central nervous system status at diagnosis, and early response to treatment (Hunger et al., 2009). The three risk categories include lower risk, higher risk, and very high risk. No published population-based studies were available to assign risk groups to children in Tanzania, Honduras, or Venezuela. Therefore, data from five consecutive ALL trials with the Berlin-Frankfurt-Munster (BFM) protocol from 1981 to 2000 were used to estimate the percentages of patients expected to fall into each risk stratum (Moricke et al., 2010). The BFM protocols enrolled 6,607 children and classified 37% as low risk, 53% medium risk, and 10% high risk. These risk group percentages were used in the forecasting model. Although the risk nomenclature for the SIOP Adapted ALL and BFM protocols vary, the criteria for the risk stratifications are similar and interchangeable.

In addition to three risk strata, the SIOP ALL Adapted Regimens includes three oncology center models which identify the optimal regimen for each patient based upon ALL risk strata and center resources (Howard et al., 2017). Setting 1 centers are described as providing limited supportive care with intensive chemotherapy regimens, resulting in an unacceptably high rate of toxic death. Setting 2 centers are described as providing intermediate supportive care, while setting 3 centers are described as resembling those in HIC.

Body Surface Area Estimates

The WHO and CDC growth charts provided length and height and weight for males and females to calculate body surface area at 1-year intervals for patients 0-19 years of age (Centers for Disease Control and Prevention, 2010). WHO length and weight charts were used for males and females from age 0-24 months of age, while the CDC growth charts were used for males and females 3-19 years of age. WHO length and growth charts were used for infants and toddlers 0-

24 months. These growth charts are recommended and provide normative standards for breastfed children and are more consistent with the physiological description of growth in infancy. WHO growth charts do not provide data for children over 5; however, the methods for CDC and WHO growth charts are similar for children 2-5 years of age and both are based on rigorous study designs for growth assessment (Centers for Disease Control and Prevention, 2010).

Acute Lymphoblastic Leukemia Incidence Estimates

The United Nations (UN) 2019 World Populations Prospects for 2020 was used to determine the population by gender and age (United Nations, 2019). NIH, NCI, and SEER CSR 1975-2010 data determined the annual incidence of ALL by gender and age. The estimated ALL incidence rate for each age and gender was determined by multiplying the incidence rate by the population for children 0-19 years of age. The estimated dose requirement for each age and gender was determined by multiplying the SIOP ALL Adapted Regimens dosing by the body surface area calculated via the WHO and CDC growth charts.

Results

The estimated annual incidence of ALL among children and adolescents 0-19 years of age was as follows: Tanzania - 1,236; Honduras – 144; and Venezuela - 356 **(Table 3-1)**. The estimated risk stratification for Tanzania, Honduras, and Venezuela is 37% lower risk, 53% higher risk, and 10% very high risk. Previous studies have reported variations in ALL incidence across geographic regions, while recent data have shown minimal variation among countries. This minimal variation could reflect the consensus-based classification of hematologic malignancies developed by the WHO (Groves, 2017; Katz et al., 2015). Table 1depicts these differences, where the CDC estimates the incidence of ALL as 34.0 cases per 1 million children 0-19 years of age (Siegel et al., 2017). The NCI estimated the incidence of ALL as 41 cases per 1 million children aged 0-14 years of age and 17 cases per million children 15-19 years of age (Lam et al., 2019). SEER estimated the incidence of ALL for each year of age for children from 0-19 years (National Institutes of Health, 2010).

Table 3-2 depicts the forecasted maximum quantity of essential chemotherapy needed to treat every child and adolescent diagnosed with ALL without cranial irradiation (CRT) within a Step 1 medical center in Honduras, Tanzania, and Venezuela. The average milligram (mg) dosage of essential chemotherapies for one child in each country is also calculated. When the average mg of each essential chemotherapy per child was multiplied by the ALL incidence for each country, the resulting chemotherapy requirements had a variability of less than 5% for each country (see **Table 3-2** and **Tables 3-3** to **3-5**).

The four SIOP ALL Adapted Regimens are as follows. Regimen 1 requires 6 essential chemotherapies, while Regimens 2 through 4 require 9 with the addition of doxorubicin, cyclophosphamide, and cytarabine. Regimen 4 requires 687 doses of 6-mercaptopurine; 775 doses for Regimen 3; 765 for Regimen 2; and 868 for Regimen 1. Regimen 1 requires 9 doses of L-asparaginase, while regimens 2, 3, and 4 require 15 doses (**Table 3-6**).

Table 3-1. Number of children at each age group and expected cases of acute lymphoblastic leukemia in four countries

Number of children per age group	Philippines	Tanzania	Honduras	Venezuela
Children ages 0-4 years	10,616,342	9,738,602	1,017,015	2,363,409
Children ages 5-9 years	11,397,952	8,623,714	988,975	2,731,190
Children ages 10-14 years	10,906,801	7,654,580	1,023,645	2,657,796
Children ages 15-19 years	10,462,894	6,434,462	1,040,990	2,500,772
Total Childhood Population 2020	43,383,989	32,451,358	4,070,625	10,253,167
Expected cases of ALL each year (SEER)	1,523	1,236	144	356
Expected cases of ALL each year (NCI) and percentage difference from SEER	1,528 (0.3%)	1176 (-4.8%)	142 (-1.2%)	360 (1.1%)
Expected cases of ALL each year (CDC) and percentage difference from SEER	1475/-3.1%	1103/-10.7%	138/-3.6%	349/2.2%

Notes: Total Childhood Population from the United Nations World Population Prospects https://population.un.org/wpp/Download/Standard/Population/
ALL — Acute lymphoblastic leukemia; SEER — Surveillance, Epidemiology, and End Results; NCI — National Cancer Institute; CDC – Centers for Disease Control and Prevention. SEER Incidence determined via yearly intervals https://seer.cancer.gov/archive/csr/1975_2010/browse_csr.php?sectionSEL=28&pageSEL=sect_28_table.13.html. NCI, Expected incidence of 41 cases per 1 million for ages 0-14, and 17 cases per 1 million for ages 15-19 retrieved from https://www.cancer.gov/types/leukemia/hp/child-all-treatment-pdq#cit/section_1.4. CDC, Expected incidence of 34 cases per 1 million retrieved from https://www.cdc.gov/mmwr/volumes/66/wr/mm6636a3.htm#T1_down

Table 3-2. Forecasted quantities of each essential medication required to deliver the SIOP Adapted ALL Regimen Level 1 without cranial radiation in three countries

Medication	Country	Medication per model	Average medication amount per child by country	Average child for the three countries (standard deviation)	Forecast of medication needed using an average from three countries	Percent difference
Prednisone (mg)	Tanzania	1,345,573	1,089	1,140 (44)	1,408,628	-4
	Venezuela	417,200	1,171		405,721	3
	Honduras	166,463	1,159		164,112	1
Vincristine (mg)	Tanzania	53,721	43	46 (2)	56,444	-5
	Venezuela	16,746	47		16,257	3
	Honduras	6,758	47		6,576	3
L-asparaginase (international units)	Tanzania	55,893,017	45,231	47,336 (1,839)	58,507,708	-4
	Venezuela	17,329,852	48,626		16,851,735	3
	Honduras	6,914,616	48,152		6,816,432	1
Intrathecal methotrexate (mg)	Tanzania	296,573	240	240 (0)	296,640	0
	Venezuela	85,534	240		85,440	0
	Honduras	34,464	240		34,560	0
Methotrexate oral (mg)	Tanzania	2,194,318	1,776	1,858 (72)	2,296,900	-4
	Venezuela	680,357	1,909		661,567	3
	Honduras	271,463	1,890		267,600	1
Methotrexate IV (mg)	Tanzania	0	0	0 (0)	0	0
	Venezuela	0	0		0	0
	Honduras	0	0		0	0
Dexamethasone (mg)	Tanzania	931,550	754	789 (31)	975,204	-4
	Venezuela	288,831	810		280,884	3
	Honduras	115,244	803		113,616	1
Mercaptopurine (mg)	Tanzania	67,382,137	54,529	57,067 (2,216)	70,534,400	-4
	Venezuela	20,892,099	58,621		20,315,733	3
	Honduras	8,335,953	58,050		8,217,600	1
Doxorubicin (mg)	Tanzania	0	0	0 (0)	0	0
	Venezuela	0	0		0	0
	Honduras	0	0		0	0

Table 3-2. (Continued)

Medication	Country	Medication per model	Average medication amount per child by country	Average child for the three countries (standard deviation)	Forecast of medication needed using an average from three countries	Percent difference
Cyclophosphamide(mg)	Tanzania	0	0	0 (0)	0	0
	Venezuela	0	0		0	0
	Honduras	0	0		0	0
Cytarabine (mg)	Tanzania	0	0	0 (0)	0	0
	Venezuela	0	0		0	0
	Honduras	0	0		0	0

Notes: SIOP – International Society of Paediatric Oncology; ALL – Acute lymphoblastic leukemia; mg – Milligrams; IV – Intravenous

Table 3-3. Forecasted quantities of each essential medication required to deliver the SIOP Adapted ALL Regimen Level 1 with cranial radiation in three countries

Medication	Country	Medication per model	Average medication amount per child by country	Average child for the three countries (standard deviation)	Forecast of medication needed using an average from three countries	Percent difference
Prednisone (mg)	Tanzania	1,345,573	1,089	1,140 (44)	1,408,628	-4
	Venezuela	417,200	1,171		405,721	3
	Honduras	166,463	1,159		164,112	1
Vincristine (mg)	Tanzania	53,721	43	46 (2)	56,444	-5
	Venezuela	16,746	47		16,257	3
	Honduras	6,758	47		6,576	3
L-asparaginase (international units)	Tanzania	55,893,017	45,231	47,336 (1,839)	58,507,708	-4
	Venezuela	17,329,852	48,626		16,851,735	3
	Honduras	6,914,616	48,152		6,816,432	1
Intrathecal methotrexate (mg)	Tanzania	259,205	210	210 (0)	259,560	0
	Venezuela	74,757	210		74,760	0
	Honduras	30,121	210		30,240	0
Methotrexate oral (mg)	Tanzania	2,246,485	1,818	1,902 (74)	2,351,284	-4
	Venezuela	696,532	1,954		677,231	3
	Honduras	277,916	1,935		273,936	1
Methotrexate IV (mg)	Tanzania	0	0	0 (0)	0	0
	Venezuela	0	0		0	0
	Honduras	0	0		0	0
Dexamethasone (mg)	Tanzania	931,550	754	789 (31)	975,204	-4
	Venezuela	288,831	810		280,884	3
	Honduras	115,244	803		113,616	1
Mercaptopurine (mg)	Tanzania	67,382,137	54,529	57,067 (2,216)	70,534,400	-4
	Venezuela	20,892,099	58,621		20,315,733	3
	Honduras	8,335,953	58,050		8,217,600	1
Doxorubicin (mg)	Tanzania	0	0	0 (0)	0	0
	Venezuela	0	0		0	0
	Honduras	0	0		0	0

Table 3-3. (Continued)

Medication	Country	Medication per model	Average medication amount per child by country	Average child for the three countries (standard deviation)	Forecast of medication needed using an average from three countries	Percent difference
Cyclophosphamide (mg)	Tanzania	0	0	0 (0)	0	0
	Venezuela	0	0		0	0
	Honduras	0	0		0	0
Cytarabine (mg)	Tanzania	0	0	0 (0)	0	0
	Venezuela	0	0		0	0
	Honduras	0	0		0	0

Notes: SIOP – International Society of Paediatric Oncology; ALL – Acute lymphoblastic leukemia; mg – Milligrams; IV – Intravenous

Table 3-4. Forecasted quantities of each essential medication required to deliver the SIOP Adapted ALL Regimen Level 2

Medication	Country	Medication Per model	Average medication amount per child by country	Average child for the three countries (standard deviation)	Forecast of medication needed using an average from three countries	Percent difference
Prednisone (mg)	Tanzania	1,632,490	1,321	1,382 (53)	1,707,740	-4
	Venezuela	506,160	1,422		491,873	3
	Honduras	201,958	1,402		198,960	2
Vincristine (mg)	Tanzania	53,362	43	45 (2)	55,620	-4
	Venezuela	16,545	46		16,020	3
	Honduras	6,602	46		6,480	2
L-asparaginase (international units)	Tanzania	79,368,084	64,214	67,175 (2,607)	83,028,300	-4
	Venezuela	24,608,389	69,125		23,914,300	3
	Honduras	9,818,754	68,186		9,673,200	2
Intrathecal methotrexate (mg)	Tanzania	309,325	250	250 (1)	309,412	0
	Venezuela	89,212	251		89,119	0
	Honduras	35,946	250		36,048	0
Methotrexate oral (mg)	Tanzania	2,020,015	1,634	1,709 (66)	2,112,736	-4
	Venezuela	626,314	1,759		608,523	3
	Honduras	249,899	1,735		246,144	2
Methotrexate IV (mg)	Tanzania	0	0	0 (0)	0	0
	Venezuela	0	0		0	0
	Honduras	0	0		0	0
Dexamethasone (mg)	Tanzania	944,592	753	796 (38)	983,856	-4
	Venezuela	292,874	823		283,376	3
	Honduras	116,857	812		114,624	2
Mercaptopurine (mg)	Tanzania	33,441,102	26,669	28,175 (1,319)	34,823,888	-4
	Venezuela	10,368,547	29,125		10,030,181	3
	Honduras	4,137,053	28,730		4,057,152	2

Table 3-4. (Continued)

Medication	Country	Medication per model	Average medication amount per child by country	Average child for the three countries (standard deviation)	Forecast of medication needed using an average from three countries	Percent difference
Doxorubicin (mg)	Tanzania	48,906	39	41 (2)	51,088	-4
	Venezuela	15,164	43		14,715	3
	Honduras	6,050	42		5,952	2
Cyclophosphamide (mg)	Tanzania	652,085	528	549 (26)	678,976	-4
	Venezuela	202,182	568		195,563	3
	Honduras	80,671	560		79,104	2
Cytarabine (mg)	Tanzania	391,251	312	330 (16)	407,468	-4
	Venezuela	121,309	341		117,361	3
	Honduras	48,402	336		47,472	2

Notes: SIOP – International Society of Paediatric Oncology; ALL – Acute lymphoblastic leukemia; mg – Milligrams; IV – Intravenous

Table 3-5. Forecasted quantities of each essential medication required to deliver the SIOP Adapted ALL Regimen Level 3

Medication	Country	Medication per model	Average medication amount per child by country	Average child for the three countries (standard deviation)	Forecast of medication needed using an average from three countries	Percent difference
Prednisone (mg)	Tanzania	1,800,997	1,457	1,524 (59)	1,884,076	-4
	Venezuela	558,406	1,569		542,663	3
	Honduras	222,804	1,547		219,504	2
Vincristine (mg)	Tanzania	52,275	42	44 (2)	54,796	-5
	Venezuela	16,208	46		15,783	3
	Honduras	6,467	45		6,384	1
L-asparaginase (international units)	Tanzania	93,155,028	75,368	78,843 (3,060)	97,450,360	-4
	Venezuela	28,883,086	81,132		28,068,227	3
	Honduras	11,524,359	80,030		11,353,440	2
Intrathecal methotrexate (mg)	Tanzania	329,641	267	267 (1)	329,600	0
	Venezuela	95,072	267		94,933	0
	Honduras	38,307	266		38,400	0
Methotrexate oral (mg)	Tanzania	1,813,418	1,467	1,535 (60)	1,896,848	-4
	Venezuela	562,257	1,579		546,341	3
	Honduras	224,341	1,558		220,992	2
Methotrexate IV (mg)	Tanzania	103,506	84	88 (3)	108,356	-4
	Venezuela	32,092	90		31,209	3
	Honduras	12,805	89		12,624	1
Dexamethasone (mg)	Tanzania	946,041	765	801 (31)	989,624	-4
	Venezuela	293,324	824		285,037	3
	Honduras	117,036	813		115,296	2
Mercaptopurine (mg)	Tanzania	13,119,333	10,614	11,104 (431)	13,724,132	-4
	Venezuela	4,067,701	11,426		3,952,905	3
	Honduras	1,623,014	11,271		1,598,928	2

Table 3-5. (Continued)

Medication	Country	Medication per model	Average medication amount per child by country	Average child for the three countries (standard deviation)	Forecast of medication needed using an average from three countries	Percent difference
Doxorubicin (mg)	Tanzania	77,629	63	66 (3)	81,576	-5
	Venezuela	24,069	68		23,496	2
	Honduras	9,604	67		9,504	1
Cyclophosphamide (mg)	Tanzania	2,339,226	1,893	1,980 (77)	2,447,280	-4
	Venezuela	725,286	2,037		704,880	3
	Honduras	289,389	2,010		285,120	1
Cytarabine (mg)	Tanzania	1,403,536	1,136	1,165 (50)	1,439,528	-3
	Venezuela	435,172	1,222		414,621	5
	Honduras	173,634	1,136		167,712	4

Notes: SIOP – International Society of Paediatric Oncology; ALL – Acute lymphoblastic leukemia; mg – Milligrams; IV – Intravenous

Table 3-6. Doses of essential medication required per SIOP Adapted ALL Protocol Regimens

Medication	Dosage	Regimen 1 doses	Regimen 1 CRT doses	Regimen 2 doses	Regimen 2 CRT doses	Regimen 3 doses	Regimen 4 doses
Prednisone	40 mg/m^2/day	22	22	0	0	0	0
Prednisone	60 mg/m$^{2/}$day	7	7	29	29	29	29
Vincristine	1.5 mg/m^2	35	35	34	34	33	36
L-asparaginase	6000 IU/m^2	9	9	15	15	15	15
Methotrexate	IT	20	16	22	18	23	19
Methotrexate	20 mg/m^2	106	110	92	96	92	48
Methotrexate	200 mg IV	0	0	0	0	0	5
Dexamethasone	6 mg/m^2/day	150	150	130	130	130	120
Dexamethasone	10 mg/m^2/day			14	14	14	14
Mercaptopurine	60 mg/m^2	0	0	15	15	15	15
Mercaptopurine	75 mg/m^2	868	868	750	750	760	672
Doxorubicin	25 mg/m^2	0	0	3	3	3	3
Cyclophosphamide	1000 mg/m^2	0	0	1	1	3	3

Table 3-6. (Continued)

Medication	Dosage	Regimen 1 doses	Regimen 1 CRT doses	Regimen 2 doses	Regimen 2 CRT doses	Regimen 3 doses	Regimen 4 doses
Cytarabine	75 mg/m^2	0	0	8	8	24	24

Notes: SIOP – International Society of Paediatric Oncology; ALL – Acute lymphoblastic leukemia; CRT – Cranial irradiation; mg – milligrams; M^2 – Square meter; IU – International Units; IT – Intrathecal; IV – Intravenous

Discussion

Summary of Findings and Strengths

This study described a forecasting model that utilizes publicly available data to estimate the quantity of essential chemotherapy needed for a child diagnosed with ALL. The goal of the UN World Populations Prospects is to provide accurate and timely population data for all countries (United Nations, 2019). WHO and CDC growth charts can be used for any country-specific initial forecasts, and country-specific ALL incidence rates do not differ dramatically from SEER incidence rates (Allemani et al.; Centers for Disease Control and Prevention, 2010; Katz et al., 2015). The SIOP Adapted ALL regimens are appropriate for all countries (Hunger et al., 2009). Understanding essential chemotherapy requirements for each regimen allows appropriate modifications of practice during times of shortages.

Implications for Practice

Our forecasting model can be of value to policy makers and healthcare providers. The forecasting model estimates the incidence of ALL and the amount of essential chemotherapy required to treat this burden. Policy makers can use this information to budget and secure the appropriate amount of essential chemotherapy within their country. Maintaining disciplined inventory levels could provide advance warnings of shortages so additional or alternative suppliers could be sourced to potentially mitigate or prevent shortages. Providers can ensure their treatment centers have an adequate supply of essential chemotherapy to treat their estimated incidence of ALL.

Limitations

Using surrogate measures of ALL incidence and growth curves to calculate doses by age and imputed percentages of each ALL risk group may introduce error in estimated chemotherapy needs. Furthermore, the UN World Populations Prospects is based upon population estimates and projections rather than the actual population, which may introduce an additional degree of error (United Nations, 2019). Patient-level data address all of these weaknesses since they directly measure incidence, rely on measurement of patients' actual height and weight rather than estimates from population curves, and take into account the treatment regimen used. However, these are not always available in LMIC where forecasting models could provide the greatest assistance. The publicly available databases used in this study do, however, provide sound forecasts for countries, regions, and centers which currently have little basis upon which to stock essential chemotherapies. Information systems are also available at no cost (e.g., www.ResonanceOncology.org) to facilitate such direct measurements and automatically calculate a patient's forecasted need prospectively as well as actual chemotherapy received by documenting each dose in the system-generated, individualized chemotherapy roadmap.

Non-specific country standard growth charts were used in calculating chemotherapy predictions and may introduce error in the estimated need. The WHO and CDC growth curves are standardized and widely utilized. However, values for children in each country inevitably differ and can even vary by regions or ethnic groups within the same country. In addition to these expected variations, we suspect that the WHO and CDC growth curves for children in LMIC, in particular, may overestimate chemotherapy needs (de Onis et al., 2010; Poskitt, 2014). For example, the WHO reported higher obesity among children in the US and more growth-stunting in LMIC, which could lead to underestimation of chemotherapy needed for children in the US and overestimation for those in LMIC (World Health Organization, 2018). Where age-specific obesity rates are known, the model could be refined, or ideally, individual patient data could be used to create accurate forecasts by patient, center, region, and country.

Future Directions – ALL Essential Chemotherapy Multipliers

Comparison of the average quantity of essential chemotherapy for each of the three countries yielded an interesting finding. It may be possible to produce a standard population-based multiplier for each essential chemotherapy, as shown in the **Appendix** for a single ALL regimen. This could allow a country or treatment center to estimate their need for each essential chemotherapy for each cancer type and regimen.

This forecasting required age-standardized incidence rates, growth curves, imputed risk stratification, and census data. Additional forecasting could be done by cancer type, chemotherapy agent, and at any level of society (individual, hospital, city, state, nation, or world). Such models can inform health policy in a manner that could facilitate access to the essential chemotherapy required and thereby eliminate needless deaths from curable cancers due to the unavailability of low-cost, essential drugs.

Forecasting national needs for essential chemotherapies for ALL is feasible using existing public data sources. Simplifying the forecasting model and applying it to a wider variety of regimens in a larger range of countries will set the stage for universal continuous supplies of essential cancer medicines. Detailed forecasting at the individual, cancer center, and regional level requires an information system with patient-level data, which can also be used to reduce other causes of preventable treatment failure like misdiagnosis, abandonment, and toxic death.

Conclusion

We found forecasting the maximum quantity of essential chemotherapies for ALL was feasible using our model, based on existing public data sources. This finding allows stakeholders including providers, cancer centers, hospitals, countries, and drug manufacturers to estimate the essential chemotherapies and to strategically manage the purchasing and inventory to treat ALL. Such knowledge may be critical to prevent or mitigate drug shortages. The model is practical and can be applied to other cancer types and treatment protocols.

CHAPTER 4. UTILIZING MULTIPLIERS TO FORECAST ESSENTIAL CHEMOTHERAPY FOR TREATMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN AND ADOLESCENTS RESIDING IN LOW- AND MIDDLE-INCOME COUNTRIES

Introduction

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer, with contemporary therapy resulting in an 85% 5-year, event-free survival and 90% overall survival in high-income countries (HIC) (Cooper & Brown, 2015; Essig et al., 2014; Jaime-Perez et al., 2016; Jeha et al., 2019). An estimated 89% of the world's children live in low- and middle-income countries (LMIC) where ALL cure rates are much lower (Allemani et al., 2015; Bhakta et al., 2013; Cooper & Brown, 2015; Jabbour et al., 2018; Jaime-Perez et al., 2016; Lam et al., 2019; Magrath et al., 2013; Pribnow et al., 2017; Redaniel et al., 2010). Causes of mortality in LMIC include non-diagnosis, incorrect or delayed diagnosis, unaffordability, abandonment and refusal of treatment, toxic death, and relapse. Preventable treatment failure may be directly related to lack of essential chemotherapy (Howard et al., 2017; Howard et al., 2007; Hsu et al., 2007; Lam et al., 2019; Simonyan et al., 2019).

The absence of accurate forecasting of essential chemotherapy demand in LMIC has been identified as a key contributor to the lack of access healthcare (Pisa & McCurdy, 2019). Rarely is disease incidence utilized in calculating the demand for essential chemotherapy (Denburg et al., 2014). A previously described forecasting model may be utilized in estimating essential chemotherapy in the treatment of childhood ALL by patient and population multipliers. First, the forecasting model incorporates available source data including incidence and body surface area by age, risk group stratification, and treatment protocols for a given country, providing an essential chemotherapy estimation (Centers for Disease Control and Prevention, 2010; Hunger et al., 2009; Moricke et al., 2010; National Institutes of Health, 2010). The patient multiplier is a given number that can be multiplied by any number of children 0-19 years of age with ALL to estimate their needed essential chemotherapy for treatment. The population multiplier is a given number that can be multiplied by a population of children 0-19 years of age to estimate the needed essential chemotherapy for the projected incidence of pediatric ALL. The aim of this study was to determine if the multipliers may be accurately derived from the forecasting model in estimating essential chemotherapy as well as determine the margin of error. This forecasting model and multiplier was applied in calculating essential chemotherapy as per the SIOP ALL treatment regimens by the annual pediatric ALL incidence rate.

Methods

Multipliers and Comparisons to Forecast Model

The forecasting multipliers were developed by a hypothetical population of 10,000,000 children evenly distributed (2.5 million each) across four 5-year interval age cohorts (0-4, 5-9,

10-14, and 15-19 years) calculated by the forecasting model projection. Patient multipliers were calculated by dividing the total chemotherapy dosage required to treat the projected ALL incidence by population (354). Population multipliers were calculated by dividing total mg of the given chemotherapy required to treat the population by the population (10,000,000).

Comparison of Outliers of Extreme Population Distributions

The forecasting model and multipliers were then applied to 171 countries with age-specific population data available in the United Nations 2017 World Populations Prospects (United Nations, 2019). Results from the forecasting model and multipliers were compared to determine differences for each country and for countries with extreme population distributions across the pediatric age range. Extreme population distributions were defined as countries with 1 or 2 standard deviations from the mean of the weighted body surface area of the 171 nations, countries with the greatest percentage of children in the 0-4 age cohort, and countries with the greatest percentage of children in the 15-19 age cohort.

Brazil was 1 standard deviation from the mean of the weighted body surface area of the 171 nations and was utilized to determine the differences between the multipliers and forecasting model for countries 1 standard deviation from the mean of the weighted body surface. Kazakhstan was 2 standard deviations from the mean of the weighted body surface area of the 171 nations and was utilized to determine the difference between the multipliers and forecasting model for countries 2 standard deviations from the mean of the weighted body surface area. Niger had the greatest percentage of children within the 0-4 age cohort and was utilized to determine the difference between the multipliers and forecasting model for countries with the greatest percentage of children in the 0-4 age cohort. Albania had the greatest percentage of children within the 15-19 age cohort and was utilized to determine the difference between the multipliers and forecasting model for countries with the greatest percentage of children within the 15-19 age cohort.

Maximum and Minimum Estimates

Maximum chemotherapy estimates assume completed treatment of pediatric ALL according to the SIOP Adapted ALL Treatment Regimens. Minimum estimates assume treatment failures secondary to incorrect or delayed diagnosis, unaffordability, abandonment and refusal of treatment, and relapse based upon a country's World Bank categorization. The World Bank defines a gross national income per capita below $1,025 as LIC, between $1,026 and $3995 as LMIC, and between $3,996 and $12,375 as UMIC (World Bank, 2018). Minimum estimates for low-income countries assume a utilization of 26% of the total maximum estimate of the essential chemotherapies. Minimum estimates for lower middle-income countries assume a utilization of 34% of the total maximum estimate of the essential chemotherapies. Minimum estimates for upper middle-income countries assume 62% of the total maximum estimate of the essential chemotherapies.

Shelf Life and Storage Requirements

Shelf life and storage requirements were based upon prescribing information from the United States Food and Drug Administration (FDA), the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA), and the European Medicines Agency (EMA).

Results

Brazil demonstrated the difference between the multipliers and forecasting model at 1 standard deviation from the mean of the weighted body surface area of 171 nations (**Tables 4-1** to **4-4**). On two analyses, the multipliers demonstrated a greater than 2% difference from the forecasting model. At a level 1 treatment center with cranial radiation as a treatment component, the multiplier demonstrated a 3% less need for oral methotrexate than the forecasting model. At a level 3 treatment center with cranial radiation as a treatment component, the multiplier demonstrated a 4% greater need for vincristine than the forecasting model. Kazakhstan demonstrated the difference between the multipliers and forecasting model at 2 standard deviations from the mean of the weighted body surface area of the 171 nations (**Tables 4-1 to 4-4**). There were 4 times when the multipliers demonstrated greater than a 10% difference from the forecasting model. At a level 1 treatment center with and without cranial radiation, the multiplier demonstrated a 12% greater need for vincristine than the forecasting model. At a level 2 treatment center, the multiplier demonstrated a 13% greater need for vincristine than the forecasting model. At a level 3 treatment center, the multiplier demonstrated a 15% greater need for vincristine than the forecasting model.

Niger demonstrated the difference between the multipliers and the forecasting model for the country with the greatest percentage of children in the 0-4 age cohort at 34% (**Tables 4-1 to 4-4**). Vincristine was the only chemotherapy agent that had a greater than 10% difference for the multipliers and the forecasting model for Niger. At a level 1 treatment center with and without cranial radiation as a treatment component, the multiplier demonstrated a 12% greater need for vincristine than the forecasting model. At a level 2 treatment center, the multiplier demonstrated a 13% greater need for vincristine than the forecasting model. At a level 3 treatment center, the multiplier demonstrated a 15% greater need for vincristine than the forecasting model. Albania showed a difference between the multipliers and forecasting model for the country with the greatest percentage of children in the 15-19 age cohort at 32% (**Tables 4-1 to 4-4**). There were 2 times when multipliers demonstrated greater than a 6% difference from the forecasting model. At a level 1 treatment center with and without cranial radiation as a treatment component, the multiplier demonstrated a 12% less need for vincristine than the forecasting model.

Minimum and maximum multipliers for LIC, LMIC, and UMIC for each essential chemotherapy administered in the 3 described treatment centers per SIOP ALL adapted treatment regimens are depicted in **Tables 4-5** to **4-8** and shelf life and storage requirements for each essential chemotherapy (**Table 4-9**). Three chemotherapy agents require cold chain storage: L-asparaginase, oral methotrexate, and doxorubicin. Methotrexate and cytarabine oral solution have the shortest shelf life at 18 months. Additionally, methotrexate and mercaptopurine tablets both have the longest shelf life at 60 months.

Table 4-1. Difference between the multipliers and forecasting model for International Society of Paediatric Oncology Adapted Acute Lymphoblastic Leukemia Regimen Level 1 without cranial radiation in selected countries that represent extremes of age distribution

		Brazil	Kazakhstan	Niger	Albania
Medication dosage	**Reason for selection**	**One standard deviation more than the mean weighted BSA**	**Two standard deviations less than the mean weighted BSA**	**Greatest percentage of children aged 0-4 years**	**Greatest percentage of children aged 15-19 years**
Prednisone milligrams	Multiplier	2,532,464	271,583	555,901	29,807
	model	2,595,522	246,814	504,493	31,518
	% diff	2%	-9%	-9%	6%
Vincristine milligrams	Multiplier	105,245	11,287	23,102	1,239
	model	103,521	9,960	20,222	1,382
	% diff	-2%	-12%	-12%	12%
L-asparaginase (international units)	Multiplier	105,197,014	11,281,393	23,091,810	1,238,157
	model	107,814,004	10,252,286	20,955,876	1,309,203
	% diff	2%	-9%	-9%	6%
Intrathecal methotrexate milligrams	Multiplier	526,226	56,433	115,512	6,194
	model	526,226	56,433	115,512	6,194
	% diff	0%	0%	0%	
Methotrexate oral milligrams	Multiplier	4,130,876	442,998	906,769	48,620
	model	4,232,698	402,497	822,712	51,398
	% diff	2%	-9%	-9%	6%

Table 4-1. (Continued)

Medication dosage	Reason for selection	Brazil One standard deviation more than the mean weighted BSA	Kazakhstan Two standard deviations less than the mean weighted BSA	Niger Greatest percentage of children aged 0-4 years	Albania Greatest percentage of children aged 15-19 years
Dexamethasone milligrams	Multiplier	1,754,088	188,109	385,040	20,645
	model	1,796,900	170,871	349,265	21,820
	% diff	2%	-9%	-9%	6%
Mercaptopurine milligrams	Multiplier	126,820,528	13,600,312	27,838,390	1,492,663
	model	129,975,771	12,359,700	25,263,473	1,578,316
	% diff	2%	-9%	-9%	6%

Notes: BSA – Body surface area. Weighted BSA, based upon age distribution. Multiplier, Nations' estimated incidence of acute lymphoblastic leukemia was multiplied by the individual patient multiplier. Model, Each nation's drug requirement was estimated via the full predictive model. Intrathecal methotrexate, doses were rounded to 12mg.

Table 4-2. Difference between the multipliers and forecasting model for International Society of Paediatric Oncology Adapted Acute Lymphoblastic Leukemia Regimen Level 1 with cranial radiation in selected countries that represent extremes of age distribution

		Brazil	Kazakhstan	Niger	Albania
Medication dosage	Reason for selection	One standard deviation more than the mean weighted BSA	Two standard deviations less than the mean weighted BSA	Greatest percentage of children aged 0-4 years	Greatest percentage of children aged 15-19 years
Prednisone milligrams	Multiplier	2,532,464	271,583	555,901	29,807
	model	2,595,522	246,814	504,493	31,518
	% diff	2%	-9%	-9%	6%
Vincristine milligrams	Multiplier	105,245	11,287	23,102	1,239
	model	103,521	9,960	20,222	1,382
	% diff	-2%	-12%	-12%	12%
L-asparaginase (international units)	Multiplier	105,197,014	11,281,393	23,091,810	1,238,157
	model	107,814,004	10,252,286	20,955,876	1,309,203
	% diff	2%	-9%	-9%	6%
Intrathecal methotrexate milligrams	Multiplier	460,448	49,379	101,073	5,413
	model	459,922	49,322	100,957	5,413
	% diff	0%	0%	0%	0%
Methotrexate oral milligrams	Multiplier	4,227,351	453,344	927,946	49,755
	model	4,333,324	412,066	842,271	52,620
	% diff	3%	-9%	-9%	6%

Table 4-2. (Continued)

Medication dosage	Reason for selection	Brazil: One standard deviation more than the mean weighted BSA	Kazakhstan: Two standard deviations less than the mean weighted BSA	Niger: Greatest percentage of children aged 0-4 years	Albania: Greatest percentage of children aged 15-19 years
Dexamethasone milligrams	Multiplier	1,754,088	188,109	385,040	20,645
	model	1,796,900	170,871	349,265	21,820
	% diff	2%	-9%	-9%	6%
Mercaptopurine milligrams	Multiplier	126,820,528	13,600,312	27,838,390	1,492,663
	model	129,975,771	12,359,700	25,263,473	1,578,316
	% diff	2%	-9%	-9%	6%

Notes: BSA – Body surface area. Weighted BSA, based upon age distribution. Multiplier, Nations' estimated incidence of acute lymphoblastic leukemia was multiplied by the individual patient multiplier. Model, each nation's drug requirement was estimated via the full predictive model. For Intrathecal methotrexate, doses were rounded to 12mg.

Table 4-3. Difference between the multipliers and forecasting model for International Society of Paediatric Oncology Adapted Acute Lymphoblastic Leukemia Regimen Level 2 in selected countries that represent extremes of age distribution

		Brazil	Kazakhstan	Niger	Albania
Medication dosage	**Reason for selection**	**1 standard deviation more than the mean weighted BSA**	**2 standard deviations less than the mean weighted BSA**	**Greatest percentage of children aged 0-4 years**	**Greatest percentage of children aged 15-19 years**
Prednisone milligrams	Multiplier	3,091,579	331,543	678,633	36,388
	model	3,148,968	299,443	612,067	38,238
	% diff	2%	-10%	-10%	5%
Vincristine milligrams	Multiplier	105,245	11,287	23,102	1,239
	model	102,932	9,788	20,007	1,250
	% diff	-2%	-13%	-13%	1%
L-asparaginase (international units)	Multiplier	149,378,094	16,019,399	32,790,004	1,758,163
	model	153,095,885	14,558,246	29,757,344	1,859,068
	% diff	2%	-9%	-9%	6%
Intrathecal methotrexate milligrams	Multiplier	548,152	58,784	120,325	6,452
	model	548,854	58,859	120,479	6,460
	% diff	0%	0%	0%	0%
Methotrexate Oral milligrams	Multiplier	3,801,985	407,727	834,574	44,749
	model	3,896,478	370,525	757,361	47,316
	% diff	2%	-9%	-9%	6%
Dexamethasone milligrams	Multiplier	1,778,206	190,696	390,334	20,929
	model	1,822,057	173,264	354,154	22,126
	% diff	2%	-9%	-9%	6%

Table 4-3. (Continued)

Medication dosage	Reason for selection	Brazil 1 standard deviation more than the mean weighted BSA	Kazakhstan 2 standard deviations less than the mean weighted BSA	Niger Greatest percentage of children aged 0-4 years	Albania Greatest percentage of children aged 15-19 years
Mercaptopurine milligrams	Multiplier	62,938,853	6,749,601	13,815,715	740,783
	model	64,505,717	6,134,000	12,538,017	783,303
	% diff	2%	-9%	-9%	6%
Doxorubicin milligrams	Multiplier	92,090	9,876	20,215	1,084
	model	94,337	8,971	18,336	1,146
	% diff	2%	-9%	-9%	6%
Cyclophosphamide milligrams	Multiplier	1,227,861	131,677	269,528	14,452
	model	1,257,830	119,610	244,485	15,274
	% diff	2%	-9%	-9%	6%
Cytarabine milligrams	Multiplier	736,717	79,006	161,717	8,671
	model	754,698	71,766	146,691	9,164
	% diff	2%	-9%	-9%	6%

Notes: BSA – Body surface area. Weighted BSA, based upon age distribution. Multiplier, Nations' estimated incidence of acute lymphoblastic leukemia was multiplied by the individual patient multiplier. Model, each nation's drug requirement was estimated via the full predictive model. For Intrathecal methotrexate, doses were rounded to 12mg.

Table 4-4. Difference between the multipliers and forecasting model for International Society of Paediatric Oncology Adapted Acute Lymphoblastic Leukemia Regimen Level 3 in selected countries that represent extremes of age distribution

		Brazil	Kazakhstan	Niger	Albania
Medication dosage	**Reason for selection**	**1 standard deviation more than the mean weighted BSA**	**2 standard deviations less than the mean weighted BSA**	**Greatest percentage of children aged 0-4 years**	**Greatest percentage of children aged 15-19 years**
Prednisone milligrams	Multiplier	3,389,774	363,521	744,090	39,897
	model	3,474,007	330,351	675,245	42,185
	% diff	2%	-9%	-9%	6%
Vincristine milligrams	Multiplier	105,245	11,287	23,102	6,890
	model	100,836	9,589	19,600	1,224
	% diff	-4%	-15%	-15%	-1%
L-asparaginase (international units)	Multiplier	175,327,626	18,802,243	38,486,189	2,063,586
	model	179,690,006	17,087,143	34,926,460	2,182,004
	% diff	2%	-9%	-9%	6%
Intrathecal methotrexate milligrams	Multiplier	585,427	62,782	128,507	6,890
	model	584,900	62,725	128,392	6,884
	% diff	0%	0%	0%	0%
Methotrexate oral milligrams	Multiplier	3,413,893	366,108	749,384	40,181
	model	3,497,965	332,630	679,902	42,476
	% diff	2%	-9%	-9%	6%
Methotrexate IV milligrams	Multiplier	195,142	20,927	42,836	2,297
	model	199,656	18,986	38,807	2,424
	% diff	2%	-9%	-9%	6%

Table 4-4. (Continued)

Medication dosage	Reason for selection	Brazil 1 standard deviation more than the mean weighted BSA	Kazakhstan 2 standard deviations less than the mean weighted BSA	Niger Greatest percentage of children aged 0-4 years	Albania Greatest percentage of children aged 15-19 years
Dexamethasone milligrams	Multiplier	1,780,399	190,931	390,816	20,955
	model	1,824,852	173,529	354,698	22,159
	% diff	2%	-9%	-9%	6%
Mercaptopurine milligrams	Multiplier	24,690,975	2,647,875	5,419,919	290,610
	model	25,306,343	2,406,439	4,918,810	307,299
	% diff	2%	-9%	-9%	6%
Doxorubicin milligrams	Multiplier	146,905	15,754	32,247	1,729
	model	149,742	14,239	29,105	1,818
	% diff	2%	-10%	-10%	5%
Cyclophosphamide milligrams	Multiplier	4,402,760	472,155	966,450	51,820
	model	4,512,216	429,077	877,042	54,793
	% diff	2%	-9%	-9%	6%
Cytarabine milligrams	Multiplier	2,642,094	283,340	579,966	31,097
	model	2,707,329	257,446	526,225	32,876
	% diff	2%	-9%	-9%	6%

Notes: BSA – Body surface area. Weighted BSA, based upon age distribution. Multiplier, Nations' estimated incidence of acute lymphoblastic leukemia was multiplied by the individual patient multiplier. Model, each nation's drug requirement was estimated via the full predictive model. Intrathecal methotrexate, doses were rounded to 12mg

Table 4-5. Patient and population multipliers for International Society of Paediatric Oncology Adapted Acute Lymphoblastic Leukemia Regimen Level 1 without cranial radiation

Medication	Multiplier	LIC minimum	LIC maximum	LIC minimum	LIC maximum	LIC minimum	LIC maximum
Prednisone milligrams	Patient	300	1,155	393	1,155	716	1,155
	Population	0.0106	0.0409	0.0139	0.0409	0.0254	0.0409
Vincristine milligrams	Patient	12	48	16	48	30	48
	Population	0.0004	0.0016	0.00054	0.0016	0.0010	0.0016
L-asparaginase international units	Patient	12,474	47,978	16,313	47,978	29,746	47,978
	Population	0.4416	1.6984	0.5775	1.6984	1.0530	1.6984
Methotrexate IT milligrams	Patient	62	240	82	240	149	240
	Population	0.0022	0.0085	0.0029	0.0085	0.0053	0.0085
Methotrexate oral milligrams	Patient	490	1,884	641	1,884	1,168	1,884
	Population	0.0173	0.0667	0.0227	0.0667	0.0414	0.0667
Methotrexate IV milligrams	Patient						
	Population						
Dexamethasone milligrams	Patient	208	800	272	800	496	800
	Population	0.0074	0.0283	0.0096	0.0283	0.0175	0.0283
Mercaptopurine milligrams	Patient	15,038	57,840	19,666	57,840	35,861	57,840
	Population	0.5324	2.0475	0.6962	2.0475	1.2695	2.0475
Doxorubicin milligrams	Patient						
	Population						

Table 4-5. (Continued)

Medication	Multiplier	LIC minimum	LIC maximum	LIC minimum	LIC maximum	LIC minimum	LIC maximum
Cyclophosphamide milligrams	Patient Population						
Cytarabine milligrams	Patient Population						

Notes: LIC – Low-income-country; LMIC – Low-middle-income-country; UMIC – Upper middle-income-country; IT – Intrathecal; IV – Intravenous. Patient, Individual patient multiplier. Population, Population multiplier.

Table 4-6. Patient and population multipliers for International Society of Paediatric Oncology Adapted Acute Lymphoblastic Leukemia Regimen Level 1 with cranial radiation

Medication	Multiplier	LIC minimum	LIC maximum	LIC minimum	LIC maximum	LIC minimum	LIC maximum
Prednisone milligrams	Patient	300	1,155	393	1,155	716	1,155
	Population	0.0106	0.0409	0.0139	0.0409	0.0254	0.0409
Vincristine milligrams	Patient	12	48	16	48	30	48
	Population	0.0004	0.0016	0.00054	0.0016	0.0010	0.0016
L-asparaginase international units	Patient	12,474	47,978	16,313	47,978	29,746	47,978
	Population	0.4416	1.6984	0.5775	1.6984	1.0530	1.6984
Methotrexate IT milligrams	Patient	55	210	71	210	130	210
	Population	0.0019	0.0074	0.0025	0.0074	0.0046	0.0074
Methotrexate Oral milligrams	Patient	501	1,928	656	1,928	1,195	1,928
	Population	0.0178	0.0683	0.0232	0.0683	0.0423	0.0683
Methotrexate IV milligrams	Patient						
	Population						
Dexamethasone milligrams	Patient	208	800	272	800	496	800
	Population	0.0074	0.0283	0.0175	0.0283	0.0175	0.0283
Mercaptopurine milligrams	Patient	15,038	57,840	19,666	57,840	35,861	57,840
	Population	0.5324	2.0475	0.6962	2.0475	1.2695	2.0475
Doxorubicin milligrams	Patient						
	Population						

Table 4-6. (Continued)

Medication	Multiplier	LIC minimum	LIC maximum	LIC minimum	LIC maximum	LIC minimum	LIC maximum
Cyclophosphamide milligrams	Patient Population						
Cytarabine milligrams	Patient Population						

Notes: LIC – Low-income-country; LMIC – Low-middle-income-country; UMIC – Upper middle-income-country; IT – Intrathecal; IV – Intravenous. Patient, Individual patient multiplier; Population, Population multiplier

Table 4-7. Patient and population multipliers for International Society of Paediatric Oncology Adapted Acute Lymphoblastic Leukemia Regimen Level 2 with cranial radiation

Medication	Multiplier	LIC minimum	LIC maximum	LIC minimum	LIC maximum	LIC minimum	LIC maximum
Prednisone milligrams	Patient	364	1,401	476	1,401	869	1,401
	Population	0.0129	0.0496	0.0169	0.0496	0.0308	0.0496
Vincristine milligrams	Patient	12	48	16	48	30	48
	Population	0.0004	0.0016	0.00054	0.0016	0.0010	0.0016
L-asparaginase international units	Patient	17,713	68,128	23,164	68,128	42,239	68,128
	Population	0.6270	2.4117	0.8200	2.4117	1.4953	2.4117
Methotrexate IT milligrams	Patient	65	250	85	250	155	250
	Population	0.0023	0.0089	0.0030	0.0089	0.0055	0.0089
Methotrexate Oral milligrams	Patient	451	1,734	590	1,734	1,075	1,734
	Population	0.0160	0.0614	0.0209	0.0614	0.0381	0.0614
Methotrexate IV milligrams	Patient						
	Population						
Dexamethasone milligrams	Patient	211	811	276	811	503	811
	Population	0.0075	0.0287	0.0178	0.0287	0.0178	0.0287
Mercaptopurine milligrams	Patient	7,463	28,705	9,760	28,705	17,797	28,705
	Population	0.2642	1.0162	0.3455	1.0162	0.6300	1.0162
Doxorubicin milligrams	Patient	11	42	14	42	26	42
	Population	0.0004	0.0015	0.0005	0.0015	0.0009	0.0015

Table 4-7. (Continued)

Medication	Multiplier	LIC minimum	LIC maximum	LIC minimum	LIC maximum	LIC minimum	LIC maximum
Cyclophosphamide milligrams	Patient	146	560	190	560	347	560
	Population	0.0051	0.0198	0.0067	0.0198	0.0123	0.0198
Cytarabine milligrams	Patient	87	336	114	336	208	336
	Population	0.0031	0.0119	0.0040	0.0119	0.0074	0.0119

Notes: LIC – Low-income-country; LMIC – Low-middle-income-country; UMIC – Upper middle-income-country; IT – Intrathecal; IV – Intravenous. Patient, Individual patient multiplier. Population, Population multiplier.

Table 4-8. Patient and population multipliers for International Society of Paediatric Oncology Adapted Acute Lymphoblastic Leukemia Regimen Level 3

Medication	Multiplier	LIC minimum	LIC maximum	LIC minimum	LIC maximum	LIC minimum	LIC maximum
Prednisone milligrams	Patient	402	1,546	526	1,546	959	1,546
	Population	0.0142	0.0547	0.0186	0.0547	0.0339	0.0547
Vincristine milligrams	Patient	12	45	15	45	28	45
	Population	0.0004	0.0016	0.0005	0.0016	0.0010	0.0016
L-asparaginase international units	Patient	20,790	79,963	27,187	79,963	49,577	79,963
	Population	0.7360	2.8307	0.9624	2.8307	1.7550	2.8307
Methotrexate IT milligrams	Patient	69	267	91	267	166	267
	Population	0.0024	0.0094	0.0032	0.0094	0.0058	0.0094
Methotrexate Oral milligrams	Patient	405	1,557	529	1,557	965	1,557
	Population	0.0143	0.0551	0.0187	0.0551	0.0342	0.0551
Methotrexate IV milligrams	Patient	23	89	30	89	55	89
	Population	0.0008	0.0031	0.0011	0.0031	0.0019	0.0031
Dexamethasone milligrams	Patient	211	812	276	812	503	812
	Population	0.0075	0.0287	0.0098	0.0287	0.0178	0.0287
Mercaptopurine milligrams	Patient	2,928	11,261	3,829	11,261	6,982	11,261
	Population	0.1037	0.3987	0.1356	0.3987	0.2472	0.3987
Doxorubicin milligrams	Patient	17	67	23	67	42	67
	Population	0.0006	0.0024	0.0008	0.0024	0.0015	0.0024

Table 4-8. (Continued)

Medication	Multiplier	LIC minimum	LIC maximum	LIC minimum	LIC maximum	LIC minimum	LIC maximum
Cyclophosphamide milligrams	Patient	522	2008	683	2008	1,245	2008
	Population	0.0185	0.0711	0.0242	0.0711	0.0441	0.0711
Cytarabine milligrams	Patient	313	1205	410	1205	747	1205
	Population	0.0111	0.0426	0.0145	0.0426	0.0264	0.0426

Notes: LIC – Low-income-country; LMIC – Low-middle-income-country; UMIC – Upper middle-income-country; IT – Intrathecal; IV – Intravenous. Patient, Individual patient multiplier. Population, Population multiplier.

Table 4-9. Shelf life and storage requirements for medications used to treat acute lymphoblastic leukemia with the International Society of Paediatric Oncology Regimens

Medication	Form	Route	Shelf life	Special instructions	Storage requirements	Temperature range (degrees Celsius)
Prednisone	Tablets	Oral	36 Months	Protect from light and moisture	Room temperature	15 to 25
Vincristine	Solution	IV	24 Months	Protect from light	Cold chain	2 to 8
L-asparaginase	Solution or powder	IV or IM	36 Months	Neutral glass vial	Cold chain	2 to 8
PEG-asparaginase (Oncaspar)	Solution	IV or IM	8 Months	Do not shake or freeze, protect from light	Cold chain	2 to 8
PEG-asparaginase (Oncaspar)	Powder	IV or IM	3 Years	Do not freeze	Cold chain	2 to 8
Methotrexate	Tablets	Oral	36 or 60 Months	None	Room temperature	20 to 25
Methotrexate	Solution	IV or IM	24 Months	Protect from light	Room temperature	15 to 25
Methotrexate	Oral solution	Oral	18 Months	Protect from light	Cold chain	2 to 8
Dexamethasone	Tablets	Oral	36 Months	Protect from light	Room temperature	20 to 25

Table 4-9. (Continued)

Medication	Form	Route	Shelf Life	Special instructions	Storage requirements	Temperature Range (degrees Celsius)
Dexamethasone	Solution	IV	21 Months	Protect from light	Room temperature	20 to 25
Mercaptopurine	Tablets	Oral	60 Months	Protect from moisture	Room temperature	15 to 25
Mercaptopurine	Oral suspension	Oral	15 Months	Protect from moisture	Room temperature	15 to 25
Doxorubicin	Solution	IV	24 Months	Refrigerate	Cold chain	2 to 8
Cyclophosphamide	Tablets	Oral	36 Months	Protect from temperatures above 25C	Room temperature	15 to 25
Cyclophosphamide	Solution or powder	IV	24 Months	Protect from temperatures above 25C	Room temperature	15 to 25
Cytarabine	Solution for infusion or injection	IV	18 Months	Should not be refrigerated	Room temperature	20 to 25

Note: Data adapted from U.S. Food & Drug Administration. (2018). Drugs@FDA: FDA-Approved Drugs. Retrieved from https://www.accessdata.fda.gov/scripts/cder/daf/ and Electronic Medicines Compendium. (n.d.). Latest Medicine Updates. Retrieved from https://www.medicines.org.uk/emc/.

Discussion

This study described multipliers derived from a forecasting model that utilizes publicly available data to estimate the quantity of essential chemotherapy needed for a child diagnosed with ALL. The goal of the UN World Populations Prospects is to provide accurate and timely population data for all countries (United Nations, 2019). WHO and CDC growth charts can be used for any country-specific initial forecasts, and country-specific ALL incidence rates do not differ dramatically from SEER incidence rates (Allemani et al.; Centers for Disease Control and Prevention, 2010; Katz et al., 2015). The SIOP Adapted ALL Regimens are appropriate for all countries (Hunger et al., 2009). Understanding essential chemotherapy requirements for each regimen allows appropriate modifications of practice during times of shortages.

Implications for Practice

If a country's childhood population is evenly distributed across the 4 age cohorts (25% 0-4 years, 25% 5-9 years, 25% 10-14 years, and 25% 15-19 years), then the country's weighted body surface area average will be 1.09. In such a case, there would not be a difference between the estimated essential chemotherapy of the forecasting model for that country and the patient and population multipliers. The multipliers did not show variations greater than 15% from the forecasting model, making multipliers valuable to healthcare providers and policy makers. Healthcare providers can use the multipliers to quickly establish and adjust their daily, weekly, or monthly need of essential chemotherapy for their treatment center. Then based upon the storage capacity of their facility, they can determine the amount of essential chemotherapy to maintain in inventory and the amount and frequency at which to order essential chemotherapy.

Policy makers could ensure their country has a national Essential Medicines List (EML) that is updated every 2 years and contains all essential chemotherapy listed according to the WHO and SIOP list of essential medications. This is recognized as an important step for procurement and availability of essential chemotherapy for LMIC (Barr & Robertson, 2016). It is important for policy makers to understand that maintaining appropriate inventory levels, regular buying patterns, and ensuring storage requirements have increased children's access to essential chemotherapy and reduced acquisition cost (Denburg et al., 2014; Moye-Holz et al., 2017). With this understanding, supply chain procedures can be put in place to ensure that a supply of the minimum estimate of the 9 essential chemotherapies to treat ALL is maintained in-country by monthly ordering patterns from multiple sources. The minimum multipliers could be utilized to establish the initial inventory levels.

Limitations

The multipliers were based on surrogate measures of ALL incidence and growth curves to calculate doses by age and imputed percentages of each ALL risk group, which may introduce error in estimated chemotherapy needs. Furthermore, the UN World Populations Prospects is based upon population estimates and projections rather than the actual population which introduces an additional degree of error (United Nations, 2019). Patient-level data addressed all

of these weaknesses since they directly measured incidence, relied on measurement of patients' actual height and weight rather than estimates from population curves, and considered the treatment regimen used. However, these are not always available in LMIC where forecasting models could provide the greatest assistance. Publicly available databases used in this study did, however, provide sound forecasts for countries, regions, and centers currently having little basis upon which to stock essential chemotherapies. Also, information systems are available at no cost (e.g., www.ResonanceOncology.org) to facilitate such direct measurements and automatically calculate a patient's forecasted need prospectively and actual chemotherapy received by documenting each dose in the system-generated, individualized chemotherapy roadmap.

Non-specific country standard growth charts were used in calculating chemotherapy forecasting and may have introduced error in the estimated need. The WHO and CDC growth curves are standardized and widely utilized. However, values for children in each country inevitably differ and can even vary by region or ethnic group within the same country. In addition to these expected variations, we suspect that the WHO and CDC growth curves for children in LMIC, in particular, may overestimate chemotherapy needs (de Onis et al., 2010; Poskitt, 2014). For example, the WHO reported higher obesity among children in the US and more growth-stunting in LMIC, which could lead to underestimation of chemotherapy needed for children in the US and overestimation for those in LMIC (World Health Organization, 2018).

Where age-specific obesity rates are known, the model could be refined, or ideally, individual patient data could be used to create accurate forecasts by patient, center, region, and country. The minimum estimates of essential chemotherapies were based upon non-diagnosis, incorrect or delayed diagnosis, unaffordability, abandonment and refusal of treatment, and relapse based upon countries' World Bank categorizations (Lam et al., 2019). Individual countries may have non-diagnosis, incorrect or delayed diagnosis, unaffordability, abandonment and refusal of treatment, and relapse rates that are less than or greater than what is typical of their World Bank categorization.

Future Directions

The established multipliers for the SIOP Adapted ALL Regimens would benefit from being examined in three ways. First, one could investigate if minimum multipliers are useful in determining in-country inventory levels and buying patterns. Second, one could also analyze if maximum multipliers are useful in estimating the 9 essential chemotherapies for individual children who complete the SIOP Adapted ALL Regimens. Last, one could example how multipliers compare to actual patient-level data utilized in information systems.

Conclusion

We found that patient and population multipliers are feasible, which allows stakeholders including providers, cancer centers, hospitals, countries, and drug manufacturers to quickly estimate essential chemotherapies for a patient or population and strategically manage their

inventory and purchasing to treat ALL. This model is practical and can be applied to other cancer types and treatment protocols.

CHAPTER 5. CONCLUSION

Summary of Findings

Lack of access to essential chemotherapy is a significant disparity for children and adolescents diagnosed with cancer in in low- and middle-income countries (LMIC) (Denburg et al., 2014; Lam et al., 2019; Moye-Holz et al., 2017; Simonyan et al., 2019). A key contributor to this disparity is the lack of accurate forecasting for the needed essential chemotherapy. My work has demonstrated that disease incidence can be utilized to forecast the needed essential chemotherapeutic agents to treat acute lymphoblastic leukemia (ALL) for a patient, center, region, and country; in the same manner, and population and patient multipliers are feasible using existing public data sources.

Strengths of Study

The National Institutes of Health (NIH), National Cancer Institute (NCI), and Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review (CSR) 1975-2010 data provided incidence rates of ALL for each year of childhood for the ages of 0 to 19 (Lam et al., 2019). Country-specific ALL incidence rates did not differ dramatically from SEER rates, especially after accounting for non-diagnosis (Katz et al., 2015; Lam et al., 2019). The International Society of Paediatric Oncology (SIOP) Adapted ALL Regimens included treatment strata appropriate for all countries (Hunger et al., 2009). If other protocols are employed within a country, they can easily be incorporated into the forecasting model. The goal of the UN World Populations Prospects is to provide accurate and timely population data for all countries (United Nations, 2019). WHO and CDC growth charts can be used for any country-specific initial forecasts (Centers for Disease Control and Prevention, 2010). If a country has its own national growth charts, they can be utilized within the forecasting model to make it even more accurate. This may be especially relevant in countries where the average height of the population differs significantly from the CDC and WHO standards or where obesity is especially prevalent or especially rare.

Weaknesses of Study

The forecasting model estimated essential chemotherapy needs based upon surrogate measures. ALL incidence, growth curves, and imputed percentages of each ALL risk group may have introduced error in the estimated essential chemotherapy forecasting. UN World Populations Prospects was based upon population estimates and projections rather than the actual population measurements from robust annual census programs, which may have introduced an additional degree of error (United Nations, 2019). However, every surrogate measure can be appropriately adjusted if and when differences become known, such as right after a recent census shows that projections from a census 10 or 20 years earlier were off by a significant amount. Although ALL incidence rates and risk groups did not vary widely, the rate of non-diagnosis was highly correlated with poverty and lack of medical infrastructure (Katz et al., 2015). This can be

addressed using estimates of non-diagnosis based on World Bank data and simulations, but such estimates do not account perfectly for non-diagnosis. The WHO and CDC growth curves are standardized and widely utilized. However, values for children in each country inevitably differ and can even vary by region or ethnic group within the same country. In addition to these expected variations, we suspected that the WHO and CDC growth curves for children in LMIC, in particular, may have overestimated chemotherapy needs (de Onis et al., 2010; Poskitt, 2014). For example, the WHO reported higher obesity among children in the US and more growth-stunting in LMIC, which could lead to underestimation of chemotherapy needed for children in the US and overestimation for those in LMIC (World Health Organization, 2018). Where age-specific differences are known, the model could be refined. However, note that because most doses of essential chemotherapeutic agents were calculated based on body surface area rather than weight, the increase in dose varied with the square root of the increase in weight, so a child who weighs 100% more than mean weight for age would require only 41% more chemotherapy. In the end, the only way to definitively address all of the above weaknesses was to include all patients in a comprehensive information system that included a cancer registry; chemotherapy regimen used; and a roadmap with each drug and dose included, patient height and weight, and patient outcomes that would preclude further therapy on the initial regimen, such as relapse, death, or abandonment.

Implications for Practice

Our forecasting model and multipliers can equip healthcare providers with information that enables them to work to ensure their patients have access to essential chemotherapy. Healthcare providers can utilize the multipliers to rapidly estimate the annual essential chemotherapy needed for their treatment center or for an individual child. The multipliers enable health care providers to continuously and appropriately adjust the required inventory levels of essential chemotherapy based upon the number of ALL patients actively being treated within the treatment center. Healthcare providers can then work within their treatment centers to ensure a process wherein appropriate inventory levels and storage requirements are met. Healthcare providers could accomplish this by partnering with treatment center administrators and appropriate staff to determine whether their facility has the capacity to maintain weekly, monthly, or quarterly inventory levels of essential chemotherapy. Healthcare providers could encourage appropriate amounts of weekly or monthly purchasing from multiple in-country sources to ensure redundancy sourcing in case one supplier is out of inventory.

Implications for Policy

The forecasting model is valuable to policy makers because it can estimate the amount of each essential chemotherapy agent required for people with ALL, and by extension, any other cancer included in the full forecasting model in the future. Policy makers can use this information to budget and secure the appropriate amount of essential chemotherapy within their country, region, city, or facility. Healthcare providers could partner with policy makers to ensure their country has a national Essential Medicines List (EML) that is updated every 2 years and contains all essential chemotherapy listed on the WHO's list of essential medications. This is

recognized as an important step for procurement and availability of essential chemotherapy for LMIC (Barr & Robertson, 2016). Maintaining in-country appropriate inventory levels from multiple sources could provide advanced warnings of shortages such that additional or alternative suppliers could be sourced to potentially prevent or mitigate shortages. Healthcare providers could help policy makers understand that maintaining appropriate inventory levels, regular buying patterns, and ensuring storage requirements have increased children's access to essential chemotherapy and reduced acquisition cost (Denburg et al., 2014; Moye-Holz et al., 2017). With this understanding, supply chain procedures can be put in place to ensure that a year's supply of the lower bound estimate of the 9 essential chemotherapy to treat ALL is maintained in-country by monthly ordering patterns from multiple sources. The lower bound multipliers could be utilized to establish the initial inventory levels.

Future Directions

The established multipliers for the SIOP Adapted ALL Regimen would benefit from being examined in three ways. First, one could investigate if the minimum and maximum multipliers are useful in determining in-country inventory levels and buying patterns. Second, one could examine if the maximum multipliers are useful in estimating the quantity utilized of the 9 essential chemotherapies for individual children who complete the SIOP Adapted ALL Regimen. Third, one could examine how the forecasting model and multipliers compare to actual patient-level data utilized in information systems like electronic medical records, registries, or research systems.

Further Guidelines for Information Systems

An information system that collects patient-level data could simultaneously create accurate forecasts and document episodes when patients lacked effective access to essential chemotherapy, which would serve as an early-warning system for drug shortages. Patient-level data allows forecasting at the individual level to assure an adequate supply for the specific patient, aggregated at the center level for use by the hospital pharmacy, and rolled up to regional and national forecasts for bulk purchasing and to facilitate procurement of adequate supplies. An information system allows documentation and appropriate adjustment to chemotherapy forecasting based upon refusal, toxic death, abandonment, and excess relapse rates.

A forecast based on patient-level information can inform governmental agencies charged with provision of a continuous supply of essential medicines and can help prevent future shortages by assuring that a 12-month supply is on hand at all times so that if a supplier leaves the market, there will be ample time to identify and onboard another. It can also be linked to health insurance coverage to assure that it corresponds to patients' needs. Most importantly, patient-level information also includes patient outcomes and can be used to improve the quality of care in real time by addressing not only drug shortages but also diagnostic delay, abandonment, toxic death, and other causes of preventable treatment failure. This approach requires robust, integrated information systems and nuanced application of national funding mechanisms.

Conclusion

More work is needed, but ALL can be cured with high-frequency and low-cost essential chemotherapy. Assuring an uninterrupted supply of essential chemotherapy is both critical and feasible. Age-standardized incidence rates, growth curves, and imputed risk stratification enable forecasting by cancer type, chemotherapy agent, and at any level of society (individual, hospital, city, state, nation, world). Such models can inform health policy and eliminate needless deaths from curable cancers due to unavailability of low-cost, essential drugs and other resources. Forecasting the maximum national needs for chemotherapeutic agents is feasible using existing public data sources. Multipliers may be useful in rapidly determining in-country and cancer treatment initial inventory levels and buying patterns. However, in-country patient-level information that includes refusal, abandonment, toxic death, and relapse is needed to estimate needs more precisely and improve all aspects of care.

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APPENDIX. STANDARD POPULATION-BASED MULTIPLIER FOR EACH ESSENTIAL CHEMOTHERAPY

Table A-1. Standard population-based multiplier for SIOP Adapted ALL Regimen Level 1 without cranial radiation in three countries

Variable	Tanzania	Honduras	Venezuela	Average	Multiplier
Number of children (age 0 to 19 years)	32,451,358	4,070,625	10,253,167	46,775,150	
Estimated children with acute lymphoblastic leukemia each year	1,236	144	356	1,736	
Prednisone/patient (rounded)	1,140	1,140	1,140	1,140	
Prednisone (mg) per country per year	1,409,040	164,160	405,840	1,979,040	Prednisone
Population multiplier (mg of prednisone per child per year)	0	0	0	0	0.0411
Vincristine/patient (rounded)	46	46	46	46	
Vincristine (mg) per country per year	56,856	6,624	16,376	79,856	Vincristine
Vincristine multiplier (mg of mercaptopurine per child per year)	0	0	0	0	0.0017
L-asparaginase/patient (rounded)	47,336	47,336	47,336	47,336	
L-asparaginase (units) per country per year	58,507,296	6,816,384	16,851,616	82,175,296	L-asparaginase

Table A-1. (Continued)

Variable	Tanzania	Honduras	Venezuela	Average	Multiplier
Population multiplier (units of L-asparaginase per child per year)	0	0	0	0	1.7070
Intrathecal methotrexate/patient (rounded)	240	240	240	240	
Intrathecal methotrexate (mg) per country per year	296,640	34,560	85,440	416,640	Methotrexate, intrathecal
Population multiplier (mg of Intrathecal methotrexate per child per year)	0	0	0	0	0.0087
Oral methotrexate/patient (rounded)	1,858	1,858	1,858	1,858	
Oral methotrexate (mg) per country per year	2,296,488	267,552	661,448	3,225,488	Methotrexate, oral
Population multiplier (mg of oral methotrexate per child per year)	0	0	0	0	0.0670
Number of children (age 0 to 19 years)	32,451,358	4,070,625	10,253,167	46,775,150	
Intravenous methotrexate/patient (rounded)	0	0	0	0	
Intravenous methotrexate (mg) per country per year	0	0	0	0	Methotrexate, intravenous

Table A-1. (Continued)

Variable	Tanzania	Honduras	Venezuela	Average	Multiplier
Population multiplier (mg of intravenous methotrexate per child per year)	0	0	0	0	0.0000
Dexamethasone/patient (rounded)	789	789	789	789	
Dexamethasone (mg) per country per year	975,204	113,616	280,884	1,369,704	Dexamethasone
Population multiplier (mg of dexamethasone per child per year)	0	0	0	0	0.0285
Mercaptopurine/patient (rounded)	57,067	57,067	57,067	57,067	
Mercaptopurine (mg) per country per year	70,534,812	8,217,648	20,315,852	99,068,312	Mercaptopurine
Population multiplier (mg of mercaptopurine per child per year)	0	0	0	0	2.0579
Doxorubicin/patient (rounded)	0	0	0	0	
Doxorubicin (mg) per country per year	0	0	0	0	Doxorubicin
Population multiplier (mg of doxorubicin per child per year)	0	0	0	0	0.0000
Cyclophosphamide/patient (rounded)	0	0	0	0	
Cyclophosphamide (mg) per country per year	0	0	0	0	Cyclophosphamide

Table A-1. (Continued)

Variable	Tanzania	Honduras	Venezuela	Average	Multiplier
Population multiplier (mg of cyclophosphamide per child per year)	0	0	0	0	0.0000
Cytarabine/patient (rounded)	0	0	0	0	
Cytarabine (mg) per country per year	0	0	0	0	Cytarabine
Number of children (age 0 to 19 years)	32,451,358	4,070,625	10,253,167	46,775,150	
Population multiplier (mg of cytarabine per child per year)	0	0	0	0	0.0000

Note: mg – Milligrams

VITA

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Brian has worked clinically as a nurse in telemetry, cardiovascular critical care, and surgery. Brian has also worked in the pharmaceutical industry as a specialty and hospital representative. He has also participated in corporate rotation assignments in the pharmaceutical industry in speaker training, customer focus groups, training, and marketing. Brian has also served in leadership capacity as an executive business manager. Brian received his Doctor of Philosophy degree in Nursing Science in May of 2020.