PEDIATRIC ONCOLOGY

Reporting Incidences of Neuroblastoma in Various Resource Settings

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PURPOSE The incidences of neuroblastoma (NB) differ significantly between various resource settings because of varying quality of cancer registries and underdiagnoses. This study aimed to evaluate current regional variations as reported by international cancer registries and the theoretical and reported differences in international NB incidences and to evaluate South Africa (SA) as a case for variable reporting.

METHODS A comprehensive literature review on registries reporting on NB was performed to construct incidence tables. The SEER Program incidence of 10.5/million children was used to calculate the expected number of NB cases for each country. Registry data of NB cases between 2000 and 2016 were requested from The South African National Cancer registry (SA-NCR) and the South African Children's Tumour Registry (SACTR) for comparison and to perform a probabilistic linkage study.

RESULTS Internationally, incidences varied between –97.1% and +80% compared with the SEER program. SA under-reported NB cases by an estimated 74.2%. Between 2000 and 2016, the SA-NCR reported between 23 and 51 cases/year, whereas the SACTR reported between 18 and 57 cases/year for the same period. The incidence reported by the SA-NCR varied between 1.5 and 2.8/million children under 15-year per year, whereas the SACTR reported 1.74-2.6 cases/million children. Both registries reported incidences less than high-income country. A probabilistic record linkage of the two registries resulted in a combined incidence of 2.9 cases/million children.

CONCLUSION As with most low- and middle-income countries, SA has either a lower incidence or underdiagnoses of NB cases. The reasons for under-reporting are not clear, but can be due to undiagnosed NB cases with spontaneous regression, missed possible cases because of lack of autopsies, and diagnosed cases not recorded in registries.

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INTRODUCTION

According to the American SEER program, the incidence of childhood malignancies between 2011 and 2015 for US children under 15-year was 16/100,000 children compared with 953 malignancies per 100,000 adults.[1] Although childhood cancers are rare, compared with adults, the childhood and adolescent incidence of malignancies will increase with growing populations.[2] Combating the increase of childhood malignancies with preventative measures is limited as there are few modifiable risk factors contributing to the etiology.[2] Concerted standardized protocol–based therapy and supportive care for children with cancer have resulted in improved survival outcomes. Yet in many countries, funding for childhood cancers constitutes a small percentage of adult cancer budgets. The planning for these health expenditures is dependent on accurate registration of disease incidences.[2] Therefore, to adequately budget for disease interventions, data to support health planning are important. Although neuroblastoma (NB) is the most common extracranial solid tumor of childhood, it only contributes to 7% of childhood malignancies.[3] It has a very heterogeneous pathophysiologic course that varies from undetected spontaneous regression to advanced metastatic disease with a high mortality, making surveillance in variable resourced settings challenging.[3]

South Africa (SA) is a provincial-based republic with a population of 58.8 million and a male:female ratio of 1.0:1.04. The country has a youthful age structure of the population with 29.2% of the population under the age of 15 years.[4] Since 2011, the Department of Health has made the registration of all malignancies compulsory. Health campaigns promoting early warning signs of childhood illness were initiated by the Department of Health and Childhood Cancer

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Why is the incidence of neuroblastoma (NB) in South Africa lower than that described in the literature and how does it compare with all the countries of the world? This study highlights the variations in reporting of NB in the world and uses South Africa as a case study to indicate possible resources to establish a true incidence of NB in a country.

Knowledge Generated

This study identifies which countries are under-reporting incidences of NB. Variations in the reported incidences are independent of resources in each country. The incidences of NB are not only dependent on tumor registries but also influenced by available clinical services, population distribution, and management systems.

Relevance

By understanding the true incidence of NB in various countries, awareness regarding rare tumors can be increased, which can be diagnosed more rapidly, and adequate resources can be allocated for treatment by policy makers.

Foundation of South Africa in 2016. The reported incidence of 45.2 per million childhood cancer cases in SA and the documented survival rates of approximately 50% are significantly lower than those in high-income countries (HICs). Although the incidence of NB is well-described in HICs, very little is known about the epidemiology of the disease in sub-Saharan Africa. In a region where communicable diseases, neonatal deaths, malnutrition, and the HIV-epidemic contribute the greatest burden to health care systems, the incidences of rare diseases, such as NB, even in the presence of disease-specific registers, are inaccurately recorded. The SEER program reported an incidence of 10.5 cases/million for NB for the United States, but a lower incidence has been recorded in low- and middle-income country (LMIC). The combination of lower reported incidences of most childhood cancers, not just NB, in LMICs and the inaccuracies of cancer registers in these regions limits the distinction between true incidences and false low values. The South African Children's Cancer Study Group (SACCSG) reported a cancer incidence of 2.7/million children younger than 15 years on the basis of data from 1987 to 2007.[5]

Two registries record cases of pediatric malignancies in SA: The South African Children's Tumour Registry (SACTR) established in 1987 by the SACCSG is a clinical-based registry compiled by data submitted by physicians treating children with childhood malignancies.[5] The registry complies with international quality standards for cancer registries. Relapses are linked with diagnostic registration and noted for future use. Cases with incomplete data are not included in reported data. The South African National Cancer Registry (SA-NCR) is the main cancer surveillance system in SA. Although it was established in 1986 as a voluntary, pathology-based cancer reporting system, the register was mandated through legislation in 2011 to monitor and report the national cancer burden.[6]

The aim of this study was (1) to evaluate the theoretical and reported differences in incidences globally and (2) to determine the incidence of NB in SA children under the age of 15 years on the basis of clinical records from pediatric oncology units (POUs) in SA and the two local South African registries.

METHODS

African Index Medicus, ScieLo, PubMed, Global Health, Embase, and Google Scholar were searched to perform a comprehensive literature review of publications with medical subject headings in line with registries reporting on NB such as registries, neuroblastoma, children, and country or territory-specific names. The search was conducted from April 2019 to January 2020. No limitations were set on the date or language, provided that English summaries or abstracts were included. Reports of tumor registries were used to construct incidence tables. If no reports were found, data were requested electronically from relevant cancer registries of each country. The percentage of children under 15 years old per population and the population under 15 years old in each country were sourced or calculated from data from the World Bank[7] and the World Factbook website.[8] The NB incidence of 10.5 cases/million children reported by the SEER Program was used to calculate the expected number of cases for each country. The analysis of international registries reporting incidence of NB was performed for comparative purposes between regions and World Bank country income classifications. Analysis of the regions without reported data was performed to determine possible common factors for the lack of reported data.

Registry data were requested from the SA-NCR and the SACTR for registered NB cases between 2000 and 2016. Cases from the two data were compared across the two data sets. As there are no common unique identifiers in both sets, record linkage was performed using probabilistic record linkage techniques with variables such as name(s), surname, date of birth, sex, and date of diagnosis to link the patients between the two sets. The probabilistic record linkage was performed using statistical software STATA 16

TABLE 1. Reported Incidences of Neuroblastoma Per Country According to World Bank Country Income Classification

Country	AIR/ASR/CIR (percentage of incidence difference from 10.5 cases/million children)	Source
LIC		
Democratic People's Republic of Korea	11.3 (+6.7)	B
Ethiopia	3.1 (–70.4)	A and B
The Gambia	0.4 (–96.2)	A and B
Guinea	0	C
Malawi	2.8 (–73.3)	A and B
Mali	2.2 (–79.0)	A and B
Niger	0.3 (–97.1)	A and B
Uganda	1.0 (–90.5)	A and B
Republic of Yemen	1.9 (–81.9)	B
Range	0-11.3 (0 to +6.7)	
Median	1.9 (–81.9)	
LMIC		
Algeria	7.2 (–31.4)	A and B
Cameroon	0.4 (–96.1)	A and B
Arab Republic of Egypt	10.1 (–3.8)	A and B
Honduras	1.6 (–84.8)	B
India	3.6 (+65.7)	B
Kenya	1.7-2.8 (–73.3 to –83.8)	A and B
Morocco	9.1-9.6 (–8.6% to –13.3)	A and B
Nigeria	1.9 (–81.9)	A and B
Pakistan	1.7 (–83.8)	B
Philippines	2.8 (–73.3)	B
Tunisia	7.7 (–26.7)	B
Vietnam	7.7 (–26.7)	B
Zimbabwe	1.4 (–86.7)	A and B
Range	0.4-10.1 (–96.1 to –3.8)	
Median	1.9 (–81.9)	
UMIC		
Argentina	8.6 (–18.0)	B
Belarus	9.3 (–11.4)	B
Botswana	2.7 (–74.3)	A
Brazil	8.4 (–20)	B
Bulgaria	7.1 (–32.3)	B
China	8.6 (–18.1)	B
Colombia	4.0 (–61.9)	B
Costa Rica	4.0 (–61.9)	B
Cuba	8.5 (–19.4)	B
Ecuador	1.9 (–81.9)	B
Islamic Republic of Iran	2.6 (–75.2)	B
Jamaica	6.8 (–35.2)	C
Jordan	9.0 (–14.2)	B
Lebanon	10.6 (+0.01)	B

(Continued on following page)

TABLE 1. Reported Incidences of Neuroblastoma Per Country According to World Bank Country Income Classification (Continued)

Country	AIR/ASR/CIR (percentage of incidence difference from 10.5 cases/million children)	Source
Libya	8.1 (–22.6)	A and B
Malaysia	6.1 (–41.9)	A and B
Mexico	3.5 (–66.7)	B
Namibia	1.2 (–88.6)	A and B
Romania	9.0 (–14.3)	B
Russian Federation	9.3-9.8 (–6.6 to 11.4)	B
South Africa	2.7 (–74.2)	A
Suriname	0.2 (–98.1)	B
Thailand	4.6 (–52.1)	B
Turkey	10.6 (+0.01)	B
Ukraine	8.2 (–21.9)	B
Range	0.2-10.6 (–98.1 to +0.01)	
Median	7.1 (–32.3)	
HIC		
Australia	11.6 (+10.5)	B
Austria	13.3 (+26.6)	B
Bahrain	9.6 (–8.5)	B
Belgium	13.4 (+27.6)	A
Bermuda	0	C
Canada	13.8 (+31.4)	A
Chile	4.2 (–60.0)	B
Croatia	13.2 (+25.7)	B
Cyprus	13.9 (+32.3)	B
Czech Republic	14.1 (+34.2)	A and C
Denmark	9.6 (–8.6)	B
Estonia	10.0 (–4.7)	B
Finland	2.9 (–72.3)	B
France	14.2 (+35.2)	B
Germany	13.7 (+30.5)	B
Greece	14.4 (+37.1)	B
Hungary	17.0 (+61.9)	B
Iceland	6.2 (–40.9)	B
Ireland	10.9 (+3.8)	B
Israel	14.6 (+39)	B
Italy	18.9 (+80)	B
Japan	15.7 (+49.5)	B
Kuwait	9.8 (–6.7)	B
Lithuania	9.8 (–6.7)	B
Malta	14.2 (+35.2)	B
Mauritius	4.1 (–60.9)	B
Netherlands	8.1 (–22.9)	B
New Caledonia	12.9 (+22.9)	B
New Zealand	11.3 (+7.6%)	B

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TABLE 1. Reported Incidences of Neuroblastoma Per Country According to World Bank Country Income Classification (Continued)

Country	AIR/ASR/CIR (percentage of incidence difference from 10.5 cases/million children)	Source
Norway	9.2 (–12.4)	B
Poland	13.9 (+32.4)	B
Portugal	10.9-16.5 (+3.8 to 57.1)	B
Qatar	6.6 (–37.1)	B
Reunion	11.1 (+5.7)	A and C
Saudi Arabia	6.3 (–40)	B
Singapore	5.9 (–43.8)	A and B
Slovak Republic	12.8 (+21.9)	B
Slovenia	9.0 (–14.2)	B
Spain	13.8-14.6 (+31.4 to 39)	B
Sweden	9.4 (–10.4)	B
Switzerland	11.7 (+11.4)	B
Taiwan	1.3 (–87.6)	B
Trinidad and Tobago	0.6 (–94.2)	B
United Kingdom	9.6 (–8.6)	B
United States	12.4 (+18.1)	A
Uruguay	11.2 (+6.7)	B
Range	0-18.9 (0 to +80)	
Median	14.1 (+34.2)	

NOTE. Data adapted.[10-23] Abbreviations: AIR, age-adjusted cancer incidence rate; ASR, age-standardized incidence rate; CIR, crude incidence rate; HIC, high-income country; LIC, low-income country; LMIC, lower-middle–income country; UMIC, upper-middle–income country. A—cancer registry B—publication C—personal communication

(StataCorp. 2017. Stata Statistical Software: StataCorp LP, College Station, TX), and the linked data set was then deidentified data. These deidentified data were further used for analysis and reporting. Incidences were calculated with data sourced from Statistics South Africa.[9] Thereafter, comparisons were made between the international incidences, previously reported SA data, SACTR, SA-NCR, and data from POUs.

RESULTS

International Registries

The systemic literature search retrieved 127 articles, abstracts, and documents on NB, which included 13 cancer registry–based reports. These included registry-based incidences from 85 countries and territories. Data requests were sent to 95 of 127 (74.8%) countries or territories without reported data, where contact details could be sourced. Excluding SA, the focus of the linking study, no electronic data were obtained.

The national incidence of NB varied between 0.2 and 18.9/million children under 15 years/year (average 7.9/million), which varied between –97.1% and 80.0% according to the 10.5/million reported by SEER data (Appendix Table A1).

The low-income countries (LICs) had a median incidence of 1.9/million children per year and a range between 0 and 11.3/million children per year. The median and range incidences for lower-middle -income countries (LMICs) were 1.9/million children per year and 0.4-10.1/million children per year, respectively. The median and range incidences for upper-middle–income countries (UMICs) were 7.1/million children per year and 0.2-10.6/million children per year, respectively. The median and range incidences for HICs were 14.1/million children per year and 0-18.9/million children per year, respectively (Table 1).

The highest percentage of countries that did not have incidences reported were from LICs (68.9%), followed by LMICs (68%), UMICs (62.5%), and HICs (42.1%; Table 2).

The South African Case Study and South African Cancer Registries

According to our hypothetical calculations on the basis of an incidence of 10.5/million children, SA should be reporting 153 new NB cases per year (Appendix Table A1) compared with the 49.25 (range 18-57) cases that have been registered in the SACTR (Fig 1). This correlates with an incidence of 2.4/million children under 15 years, which is 74.2% less than the 10.5/million that are expected. The SA-NCR reported between 23 and 51 cases/year between 2000 and 2016, whereas the SACTR reported between 18 and 57 cases/year between 2000 and 2016 (Fig 1). The variation between the two registries was between 0.3 and 0.92 cases/million (Table 3).

TABLE 2. Countries According to World Bank Income Classification Without Neuroblastoma Data

LIC ($1,035 or less/capita/year)	LMIC ($1,036-$4,045/capita/year)	UMIC ($4,046-$12,535/capita/year)	HIC ($12,536 or more)
Afghanistan	Angola	Albania	Andorra
Burkina Faso	Bangladesh	American Samoa	Antigua and Barbuda
Burundi	Benin	Armenia	Aruba
Central African Republic	Bhutan	Azerbaijan	The Bahamas
Chad	Bolivia	Belize	Barbados
Democratic Republic of the Congo	Cambodia	Bosnia and Herzegovina	British Virgin Islands
Eritrea	Cape Verde	Curacao	Brunei Darussalam
Guinea-Bissau	Comoros	Dominica	Cayman Islands
Haiti	Republic of the Congo	Dominican Republic	Channel Islands
Liberia	Cote d'Ivoire	Equatorial Guinea	Faroe Islands
Madagascar	Djibouti	Fiji	French Polynesia
Mozambique	El Salvador	Gabon	Gibraltar
Rwanda	Eswatini (Swaziland)	Georgia	Greenland
Sierra Leone	Ghana	Grenada	Guam
Somalia	Kiribati	Guatemala	Hong Kong
South Sudan	Kyrgyz Republic	Guyana	Isle of Man
Sudan	Laos	Indonesia	Latvia
Syrian Arab Republic	Lesotho	Iraq	Liechtenstein
Tajikistan	Mauritania	Kazakhstan	Luxembourg
Togo	Federated States of Micronesia	Kosovo	Monaco
	Mongolia	Maldives	Nauru
	Myanmar (Burma)	Marshall Islands	Northern Mariana Islands
	Nepal	Moldova	Oman
	Papua New Guinea	Montenegro	Palau
	Sao Tome and Principe	Nicaragua	Panama
	Senegal	North Macedonia	Puerto Rico
	Solomon Islands	Paraguay	Republic of Korea
	Sri Lanka	Peru	San Marino
	Tanzania	Samoa	Seychelles
	Timor-Leste	Serbia	St Kitts and Nevis
	Uzbekistan	St Vincent and the Grenadines	St Lucia
	Vanuatu	Tonga	St Martin
	West Bank and Gaza	Turkmenistan	Turks and Caicos Islands
	Zambia	Tuvalu	United Arab Emirates
		Venezuela, RB	US Virgin Islands
20 of 29 LIC (68.9%)	34 of 50 LMIC (68%)	35 of 56 UMIC (62.5%)	35 of 83 HIC (42.1%)

Abbreviations: HIC, high-income country; LIC, low-income country; LMIC, lower-middle–income country; UMIC, upper-middle–income country.

The Probabilistic Record Linkage Results

From the SACTR (clinical-based registry) and SA-NCR (pathology-based registry), there were 312 and 603 new cases of NB identified, respectively (Fig 2). Furthermore, 463 cases were identified from hospital-based records in POUs. From the 775 cases diagnosed in clinical services, 148 double registered cases were excluded and a further 14 cases were excluded because of insufficient data for linking purposes. Forty-seven cases were excluded from the SA-NCR who did not meet the inclusion criteria (age > 15 years). After manual revision of the probabilistic results, a further 35 duplicate cases were excluded. Of the 824 cases, 329 (39.9%) cases matched and 268 (32.5%) and 227 (27.5%) cases were exclusively identified from the SACTR and SA-NCR, respectively. The combined crude incidence for the SACTR and SA-NCR was calculated at 2.9 cases/million children under 15 years (Table 4).

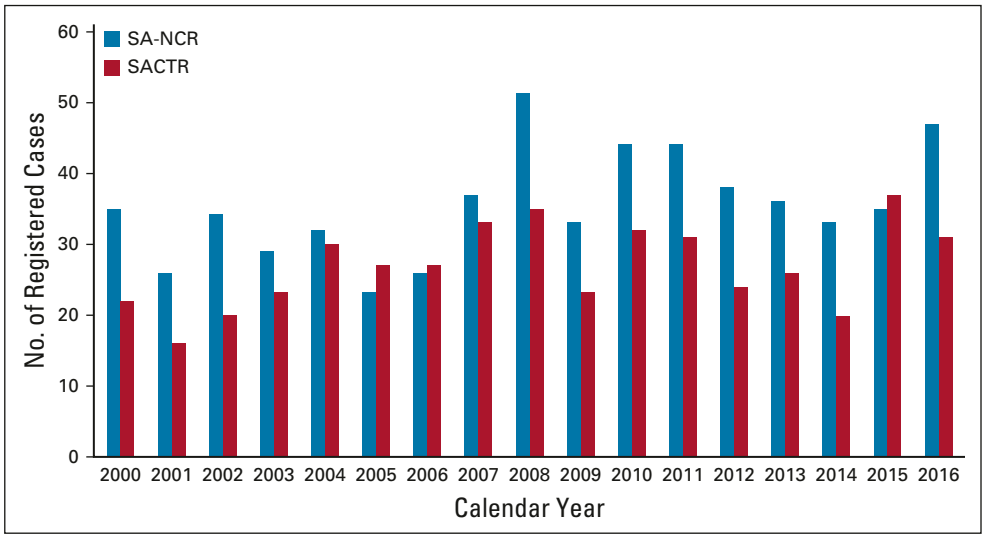

FIG 1. The discordant number of registered neuroblastoma cases in the SA-NCR and SACTR. SACTR, South African Children's Tumour Registry; SA-NCR, South African National Cancer Registry.

DISCUSSION

There is a demonstrable difference in the theoretical expected incidences and the reported incidences of NB in children under the age of 15 years. Although a higher NB incidence for children under 15 years was calculated for SA by combining several sources for reporting NB, the incidence remains far lower than that reported in HICs. The lower reported incidences of NB or absence of reported data is not only highest in LICs and LMICs but also present in UMICs and HICs.

TABLE 3. South African NB Crude Incidence Rates for Children Under the Age of 15 Years

Year	Indicator	SACTR	SA-NCR	Difference
2000	NB (No.)	39	35	0.3
	SA u15	15,084,120		
	Incidence/million children u15	2.6	2.3	
2001	NB (No.)	25	26	0.76
	SA u15	14,365,288		
	Incidence/million children u15	1.74	2.5	
2005	NB (No.)	36	23	0.9
	SA u15	15,150,381		
	Incidence/million children u15	2.4	1.5	
2010	NB (No.)	30	44	0.92
	SA u15	15,100,089		
	Incidence/million children u15	1.98	2.9	
2011	NB (No.)	34	44	0.6
	SA u15	15,812,268		
	Incidence/million children u15	2.2	2.8	
2013	NB (No.)	27	36	0.56
	SA u15	15,454,742		
	Incidence/million children u15	1.74	2.3	
2014	NB (No.)	39	33	0.4
	SA u15	15,812,268		
	Incidence/million children u15	2.4	2.0	
2016	NB (No.)	47	31	0.9
	SA u15	16,852,358		
	Incidence/million children u15	2.7	1.8	

Abbreviations: NB, neuroblastoma; SACTR, South African Children's Tumour Registry; SA-NCR, South African National Cancer Registry; SA u15, South African population under the age of 15 years.

NB is a significant cause of childhood cancer deaths and a burden on resources regardless of the country of diagnosis. When using mortality estimates to calculate disability-adjusted life years, the burden disproportionately affects populations in resource-limited settings.[24] Yet since these calculations are in part based on clinical-based, pathology-based, or population-based cancer registries, the burden might be under-represented.[24] With the heterogeneous presentation of NB, the socioeconomic impact on health services cannot be reliably determined as the national incidences are not accurately recorded.

In LMICs, reliable pediatric cancer registries are variable or are limited to single institutions.[25] This undermines the optimal interpretation of data to reflect the true burden of NB.[10,26,27] According to world-age standardized rates (WSRs), the incidence of NB should be 12% but is $< 10\%$ in Africa.[26] The WSR of 10.5 per million person-years in children in the United States is in contrast to the WSR of 2.7 per million person-years in sub-Saharan Africa.[28] In Figure 3, the current reported number of cases is reflected. The figures show a predominance of NB in westernized countries. Yet, in Figure 4, the expected number of NB cases for each country is reflected on the basis of the incidence of a WSR of 10.5 per million reported by SEER (Appendix Table A1) on the basis of the 0-year to 15-year population figures sourced from the World Bank.[7]

It is generally stated that the incidence of NB is lower in resource-limited settings.[24,25] Yet HICs, Singapore and Qatar, have incidences of 5.9 and 6.6, respectively, whereas Reunion, a French territory in sub-Saharan Africa,

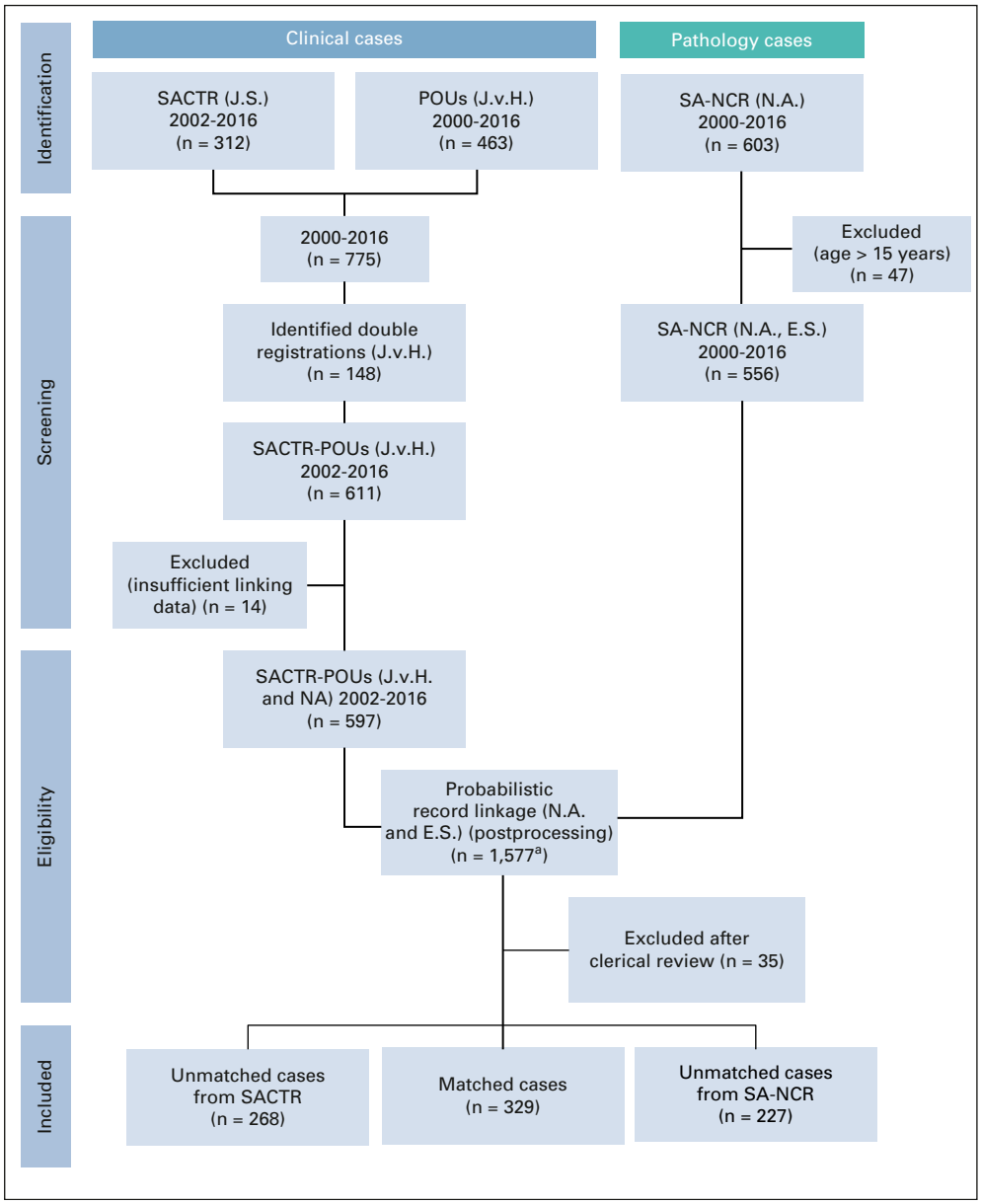

FIG 2. Methodology of the probabilistic linking study between South African pediatric oncology units, the SACTR, and the SA-NCR. POU, pediatric oncology unit; SACTR, South African Children's Tumour Registry; SA-NCR, South African National Cancer Registry. [a]Compounded number of patients including variations in spelling of names and data computations.

has an ASR incidence of 11.1/million children. This is higher than the 10.5/million children reported for the United States.[29] We postulate that Reunion, a French territory part of Africa, has the systems in place similar to France to diagnose and record cases more accurately than the rest of the African continent. The countries without reported data (Table 2) are countries where there are no pediatric oncology services and no cancer registries or no reported data could be sourced.[30] The HICs without data are predominantly islands that might not have the diagnostic services or refer pediatric oncology cases to other countries before they are diagnosed. This is also true for the South Pacific island where children are referred to Australia and New Zealand for care.[31] A landlocked country like Lichtenstein refers their pediatric oncology patients to neighboring countries. Yet this is true for Chad, a resource-limited setting, that is, a large country without services.[32] Therefore, it cannot be stated that there is a true difference in incidence between the same income-classified countries, because of a limited insight where patients are diagnosed and treated.

SA has been reporting NB incidences far lower than expected for the population size.[5] The medical system in SA is a dual public and private medical system that serves 85% and 15% of the population, respectively.[33] To evaluate the incidence of NB in the country, both the public and private medical systems should be surveilled. Innately, these two systems differ in resources, views on research, and the academic contributions to data and both clinical-based and pathology-based registries. The limitation of the SA-NCR pathology-based register system is that NB can be diagnosed on clinical signs in conjunction with radiologic

TABLE 4. Probabilistic Record Linkage Incidences: Previously Reported National and International Indices

Previously reported incidences	
International incidence (SEER data)	10.5 cases/1,000,000
National SA incidence, SACCSG (1985-2007)	2.7 cases/1,000,000
SACTR prelinkage study (2014)	2.4 cases/1,000,000
SA-NCR prelinkage study (2014)	2.0 cases/1,000,000
Probabilistic record linkage results	
SACTR, No. (%)	268 (30.7)
SA-NCR, No. (%)	277 (31.7)
Matched cases, No. (%)	329 (37.6)
Total (2014), No.	874
Population-based incidence (2014)	2.9 cases/1,000,000

Abbreviations: SA, South Africa; SACCSG, South African Children's Cancer Study Group; SACTR, The South African Children's Tumour Registry; SA-NCR, South African National cancer registry.

images and confirmed with urine catecholamine levels. Thereby, no confirmatory biopsy for evaluation in a pathology laboratory is performed. The SACTR is a clinical registry compiled by mainly pediatric oncologists in both the public and private sector. The limitation of this registry is that it excludes patients treated outside pediatric oncology units and patients who died or went undiagnosed before referral for treatment or who were misdiagnosed. Together, the two registries should account for nearly all patients who were biopsied and started with treatment in a health care facility. The incidence should reflect all diagnosed patients while minimizing patients who were not reported. Unreported cases can theoretically be sought by neonatal screening for NB and screening autopsy reports. In SA, nondiagnosis of childhood malignancies has been estimated at about 50%.[34] The undiagnosed NB cases could partly be explained by tumors that underwent maturation and remained undetected. NB screening by urine vanillylmandelic acid and homovanillic acid in infants has identified cases that would have undergone spontaneous regression.[35,36] Screening studies only proved to identify more tumors with favorable histology, but not advanced disease, nor did it improve overall survival outcomes.[35,36] By adopting a wait and see management strategy, tumor regression in untreated patients has been seen in up to 47% of patients with localized stage 1 and 2 NB.[35,36] This represents 0.7 cases/million infants screened.[37] Neonatal screening for NB has never been a policy in SA and would be too costly for a middle-income country. Sudden unexpected death because of neoplastic disease in infancy and childhood is rare.[38,39] Autopsy case series have demonstrated that a variety of neoplasms including cardiac neoplasms and CNS tumors account for the largest number of cases.[38,39] There are limited published pediatric autopsy registers available in SA to determine undiagnosed NB deaths, yet international reports concluded that NB contributed $<$ 8% of autopsy cases.[40] Therefore, these two potential sources of NB cases alone could not explain the low incidence rate in the South African population. By performing a probabilistic record linkage study on the clinical and pathologic registries, the crude incidence only increased marginally to 2.9/million children under age 15

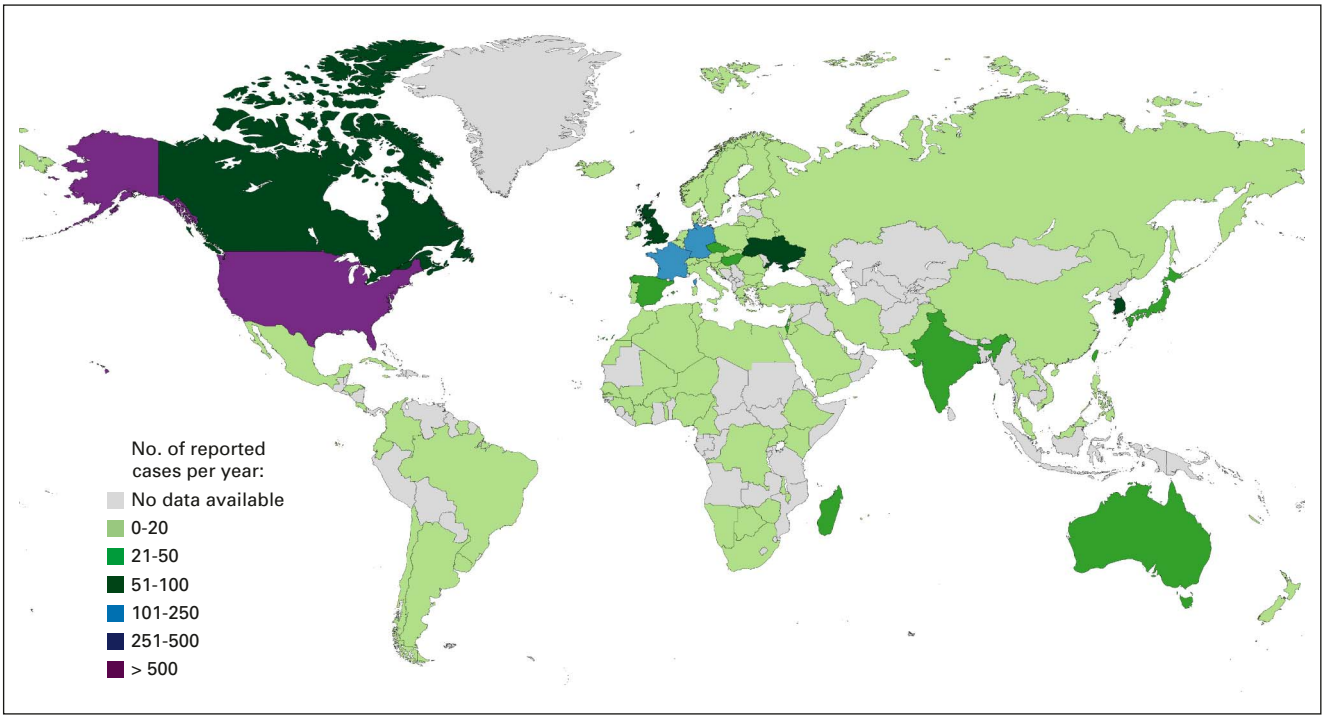

FIG 3. The number of reported cases of neuroblastoma per year in children under age 15 years.

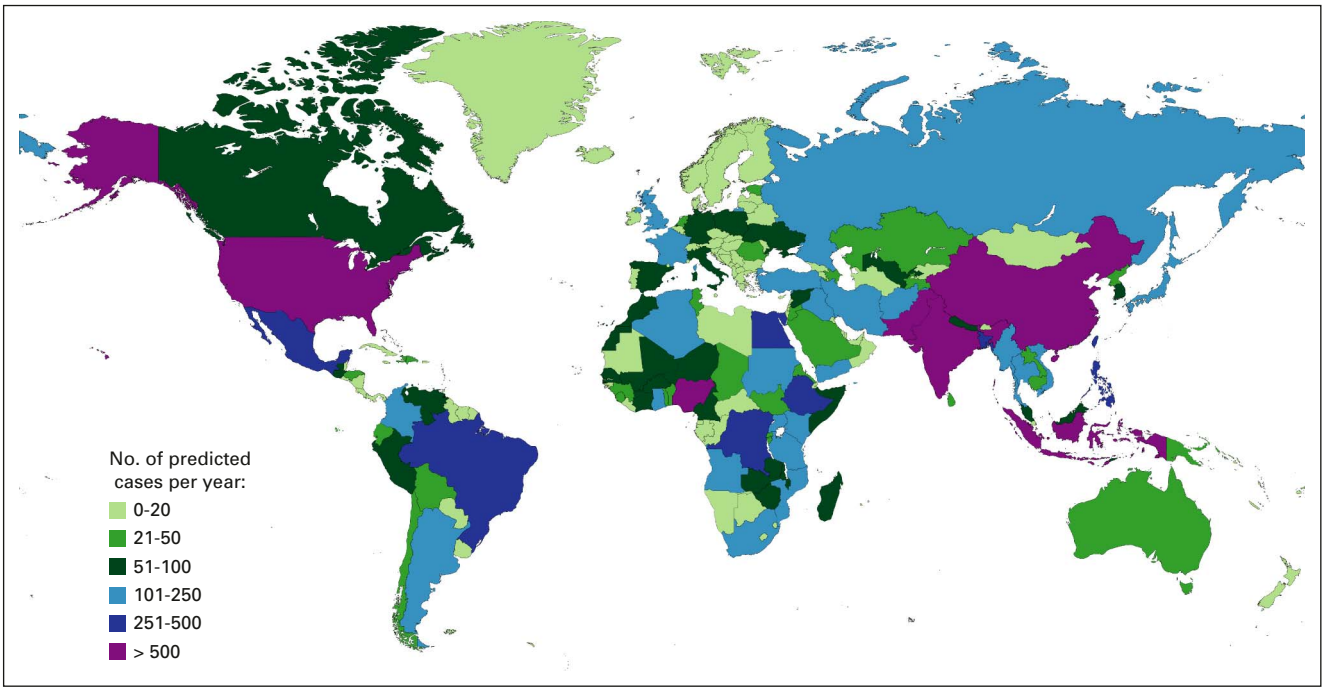

FIG 4. The number of expected cases of neuroblastoma for each country on the basis of an incidence of 10.5/million children/year.

years. This still falls short of incidences reported in higher-resource countries.

Reporting of cancers to the SA-NCR was only legally mandated in 2011. This limits the accuracy of the reports from the private health care sector. Although we expect the numbers of missed cases to be small, the recorded number may be lower. Despite the strengths of using probabilistic record linkage, there is still a possibility for false linkages or missed matches. There was no unique identifier such as national identifying number available, which is considered the gold standard for record linkage.

In conclusion, even with meticulous registration of pathologic and clinical cases of NB, undiagnosed and misdiagnosed cases will lead to under-reporting of cases in many countries. Yet SA either does under-report cases or does have a lower incidence of NB. If indeed the lower incidence is related to population characteristics, the paucity of genetic information regarding NB in LMIC may be a factor to understanding the difference in incidences. In the most likely scenario of under-reporting, increased awareness and diagnosis of childhood malignancies in SA should receive greater emphasis.

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DATA SHARING STATEMENT

Data available on request from the authors.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX

TABLE A1. Epidemiologic Characteristics of Neuroblastoma Per Country

Sub-Saharan Africa						
Country	**Percent of Children 0-14 Years Per Population (2017)[1,2]**	**Population < 0-14 Years[1,2]**	**Expected No. of Cases (10.5 per million children per year)**	**Reported No.**	**Reported No. of Cases Per Year**	**AIR/ASR/CIR (percent of incidence difference)**
Angola	47	13.99 million	130	—	—	ND
Benin	43	4.8 million	44	—	—	ND
Botswana	31	710,520	7	9 (2008-2012)	2.25	2.7 (–74.3)
Burkina Faso	45	8.635 million	81	—	—	ND
Burundi	45	4.88 million	45	—	—	ND
Cape Verde	30	163,916	1	—	—	ND
Cameroon	43	10.34 million	96	1 (2004-2006)	< 1	0.4 (–96.1)
Central African Republic	43	2.0 million	19	—	—	ND
Chad	47	5.4 million	50	—	—	ND
Comoros	40	325,564	3	—	—	ND
Democratic Republic of the Congo	46	37.41 million	350	—	—	ND
Republic of the Congo	42	2.2 million	20	—	—	ND
Cote d'Ivoire	42	10.2 million	95	—	—	ND
Djibouti	31	296,665	3	—	—	ND
Equatorial Guinea	37	469,160	4	—	—	ND
Eritrea	49	2.45 million	23	—	—	ND
Eswatini (Swaziland)	37	505,790	5	—	—	ND
Ethiopia	41	43.05 million	402	5 (2011-2013)	1.6	3.1 (–70.4)
Gabon	36	729,000	7	—	—	ND
The Gambia	45	945,450	9	3 (2002-2011)	0.33	0.4 (–96.2)
Ghana	39	11.24 million	105	—	—	ND
Guinea	42	5.3 million	50	0 (2011-2010)	0	0
Guinea-Bissau	41	763,010	7	—	—	ND
Kenya	40	19.88 million	186	19 (2007-2012)	3.8	1.7-2.8 (–73.3 to –83.8)
Lesotho	35	781,550	7	—	—	ND
Liberia	42	1.99 million	19	—	—	ND
Madagascar	41	10.48 million	98	—	—	ND
Malawi	44	5.58 million	52	9 (2003-2010)	1.125	2.8 (–73.3)
Mali	48	6.12 million	57	15 (2006-2014)	1.875	2.2 (–79.0)
Mauritius	18	227,700	2	10 (2003-2012)	1.11	4.1 (–60.9)
Mozambique	45	13.35 million	124	—	—	ND
Namibia	37	937,580	9	12 (2003-2011)	1.3	1.2 (–88.6)
Niger	50	10.74 million	100	1 (2001-2009)	0.125	0.3 (–97.1)
Nigeria	44	83.99 million	785	9 (2003-2012)	1	1.9 (–81.9)
Reunion	26	227,906	2	16 (2002-2008 and 2012)	1.28	11.1 (+5.7)
Rwanda	40	4.8 million	45	—	—	ND

(Continued on following page)

TABLE A1. Epidemiologic Characteristics of Neuroblastoma Per Country (Continued)

Country	Percent of Children 0-14 Years Per Population (2017)[1,2]	Population < 0-14 Years[1,2]	Expected No. of Cases (10.5 per million children per year)	Reported No.	Reported No. of Cases Per Year	AIR/ASR/CIR (percent of incidence difference)
Sub-Saharan Africa						
Sao Tome and Principe	43	87,860	< 1	—	—	ND
Senegal	43	6.81 million	63	—	—	ND
Seychelles	22	21,085	< 1	—	—	ND
Sierra Leone	42	3.17 million	29	—	—	ND
Somalia	46	6.78 million	63	—	—	ND
South Africa	29	16.4 million	153	197 (2008-2012)	49.25	2.7 (–74.2)
South Sudan	42	5.28 million	49	—	—	ND
Tanzania	45	25.8 million	241	—	—	ND
Sudan	41	16.6 million	155	—	—	ND
Togo	42	3.27 million	31	—	—	ND
Uganda	48	20.86 million	192	8 (2003-2012)	1	1.0 (–90.5)
Zambia	45	7.69 million	71	—	—	ND
Zimbabwe	41	6.77 million	63	7 (2003-2012)	0.78	1.4 (–86.7)
North Africa and the Middle East						
Algeria	29	11.98 million	111	112 (1996-2014)	6.2	7.2 (–31.4)
Bahrain	20	298,600	3	28 (1998-2012)	2	9.6 (–8.5)
Arab Republic of Egypt	33	32.19 million	300	133 (1999-2010)	12	10.1 (–3.8)
Islamic Republic of Iran	24	16.9 million	157	8 (2004-2011)	1	2.6 (–75.2)
Iraq	40	11.04 million	103	—	—	ND
Israel	28	1.94 million	18	568 (1990-2012)	25.8	14.6 (+39)
Jordan	36	3.49 million	33	222 (2000-2012)	18.5	9.0 (–14.2)
Libya	28	1.78 million	17	22 (2003-2008)	3.7	8.1 (–22.6)
Kuwait	21	868,770	8	61 (1994-2012)	3.4	9.8 (–6.7)
Lebanon	23	1.4 million	13	33 (2008-2010)	11	10.6 (+0.01)
Mauritania	40	1.77 million	17	—	—	ND
Morocco	27	9.64 million	90	146 (2005-2012)	20.8	9.1-9.6 (–8.6 to –13.3)
Oman	22	1.01 million	10	—	—	ND
Qatar	14	369,460	3	19 (2002-2014)	1.6	6.6 (–37.1)
Saudi Arabia	25	4.78 million	44	198 (1994-2012)	11	6.3 (–40)
Syrian Arab Republic	37	6.76 million	63	—	—	ND
Tunisia	24	2.76 million	25	121 (1993-2007)	8.6	7.7 (–26.7)
United Arab Emirates	14	1.316 million	12	—	—	ND
West Bank and Gaza	40	1.86 million	17	—	—	ND
Republic of Yemen	40	11.3 million	105	9 (1997-2006)	0.9	1.9 (–81.9)
Asia						
Afghanistan	43	15.27 million	143	—	—	ND

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TABLE A1. Epidemiologic Characteristics of Neuroblastoma Per Country (Continued)

Asia						
Armenia	20	586,000	5	—	—	ND
Azerbaijan	23	2.27 million	21	—	—	ND
Bangladesh	28	46.1 million	430	—	—	ND
Bhutan	27	218,054	< 1	—	—	ND
Brunei Darussalam	23	98,600	< 1	—	—	ND
Cambodia	31	4.96 million	46	—	—	ND
China	18	249.48 million	2,331	389 (1990-2013)	16.9	8.6 (–18.1)
Georgia	19	706,230	7	—	—	ND
Hong Kong	11	813,120	7	—	—	ND
India	28	374.9 million	3,503	526 (1990-2013)	22.9	3.6 (+65.7)
Indonesia	27	71.28 million	666	—	—	ND
Japan	13	16.5 million	154	795 (1990-2013)	34.6	15.7 (+49.5)
Kazakhstan	28	5.05 million	47	—	—	ND
Democratic People's Republic of Korea	21	5.35 million	50	1,130 (1999-2012)	86.9	11.3 (+6.7)
Republic of Korea	13	6.69 million	62	—	—	ND
Kyrgyz Republic	32	1.98 million	19	—	—	ND
Laos	33	2.26 million	21	—	—	ND
Malaysia	24	7.59 million	70	47 (2007-2011)	9.4	6.1 (–41.9)
Maldives	23	100,355	1	—	—	ND
Mongolia	30	922,800	9	—	—	ND
Myanmar (Burma)	27	14.4 million	134	—	—	ND
Nepal	31	9.08 million	84	—	—	ND
Pakistan	35	68.95 million	644	38 (1995-2012)	2.2	1.7 (–83.8)
Philippines	32	33.57 million	313	205 (1993-2012)	10.7	2.8 (–73.3)
Russian Federation	18	26.01 million	243	163 (1998-2015)	9.5	9.3-9.8 (–6.6 to 11.4)
Singapore	15	841,800	8	22 (2003-2007)	4.4	5.9 (–43.8)
Sri Lanka	24	5.15 million	48	—	—	ND
Taiwan	13	3.0 million	286	463 (1996-2010)	30.8	1.3 (–87.6)
Tajikistan	35	3.12 million	29	—	—	ND
Thailand	17	11.73 million	109	156 (1993-2013)	7.8	4.6 (–52.1)
Timor-Leste	44	570,240	53	—	—	ND
Turkey	25	19.9 million	186	134 (1993-2013)	6.7	10.6 (+0.01)
Turkmenistan	31	1.78 million	17	—	—	ND
Uzbekistan	28	9.06 million	85	—	—	ND
Vietnam	23	21.97 million	205	170 (1995-2013)	9.4	7.7 (–26.7)
Europe						
Albania	17	0.49 million	4	—	—	ND
Andorra	14	76,965	< 1	—	—	ND
Austria	14	1.22 million	11	345 (1990-2012)	15.6	13.3 (+26.6)
Belarus	17	1.61 million	15	355 (1990-2015)	14.2	9.3 (–11.4)

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TABLE A1. Epidemiologic Characteristics of Neuroblastoma Per Country (Continued)

Europe						
Belgium	17	1.92 million	18	216 (2004-2013)	11.3	13.4 (+27.6)
Bosnia and Herzegovina	14	490,980	4	—	—	ND
Bulgaria	14	994,280	9	178 (1990-2013)	7.7	7.1 (–32.3)
Channel Islands	15	24,681	< 1	—	—	ND
Croatia	15	623,100	6	113 (2000-2014)	8	13.2 (+25.7)
Cyprus	17	145,316	1	27 (1998-2013)	1.8	13.9 (+32.3)
Czech Republic	15	1.58 million	15	467 (1990-2012)	21.2	14.1 (+34.2)
Denmark	16	919,840	9	160 (1981-2000)	8	9.6 (–8.6)
Estonia	16	1.32 million	21	50 (1990-2012)	2.27	10.0 (–4.7)
Faroe Islands	20	51,095	< 1	—	—	ND
Finland	16	880,480	8	26 (1987-2003)	1.6	2.9 (—72.3)
France	18	12.09 million	113	1847 (2000-2012)	142	14.2 (+35.2)
Germany	13	10.76 million	100	2,314 (1996-2012)	136.1	13.7 (+30.5)
Gibraltar	20	34,571	< 1	—	—	ND
Greece	14	1.5 million	14	160 (2009-2016)	9.4	14.4 (+37.1)
Greenland	21	56,171	< 1	—	—	ND
Hungary	14	1.37 million	13	563 (1991-2014)	24.4	17.0 (+61.9)
Iceland	20	67,669	< 1	9 (1990-2014)	0.38	6.2 (–40.9)
Ireland	22	1.05 million	10	159 (1994-2012)	9.3	10.9 (+3.8)
Isle of Man	16	84,287	< 1	—	—	ND
Italy	14	8.48 million	79	142 (1998-2011)	10.9	18.9 (+80)
Kosovo	25	1.831	< 1	—	—	ND
Latvia	15	292,500	3	—	—	ND
Liechtenstein	15	37,810	< 1	—	—	ND
Lithuania	15	427,200	4	55 (2000-2012)	4.2	9.8 (–6.7)
Luxembourg	16	94,506	< 1	—	—	ND
Malta	14	64,441	< 1	17 (1995-2015)	0.85	14.2 (+35.2)
Moldova	16	568,000	5	—	—	ND
Monaco	10	38,695	< 1	—	—	ND
Montenegro	18	112,044	1	—	—	ND
Netherlands	16	2.73 million	26	435 (1993-2013)	20.7	8.1 (–22.9)
North Macedonia	17	350,000	3	—	—	ND
Norway	18	945,000	9	173 (1990-2013)	7.5	9.2 (–12.4)
Poland	15	5.76 million	53	111 (1999-2014)	7.4	13.9 (+32.4)
Portugal	14	1.44 million	13	227 (1990-2010)	11.35	10.9-16.5 (+3.8 to 57.1)
Romania	15	2.95 million	27	25 (2008-2012)	6.25	9.0 (–14.3)
San Marino	15	33,400	< 1	—	—	ND
Serbia	16	1.12 million	10.5	—	—	ND
Slovak Republic	15	815,250	7	122 (2000-2012)	9.3	12.8 (+21.9)
Slovenia	15	309,900	3	57 (1990-2013)	2.1	9.0 (–14.2)
Spain	15	6.98 million	65	1,011 (1990-2013)	42.1	13.8-14.6 (+31.4 to 39)
Sweden	18	1.8 million	16	291 (1990-2011)	13.2	9.4 (–10.4)

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TABLE A1. Epidemiologic Characteristics of Neuroblastoma Per Country (Continued)

Europe						
Switzerland	15	1.26 million	12	292 (1990-2013)	12.1	11.7 (+11.4)
Ukraine	15	6.724 million	62	633 (2000-2012)	52.7	8.2 (–21.9)
United Kingdom	18	11.89 million	111	1,099 (2000-2011)	91.9	9.6 (–8.6)
North America						
Antigua and Barbuda	24	24,483	< 1	—	—	ND
Aruba	18	18,947	< 1	—	—	ND
The Bahamas	20	79,072	< 1	—	—	ND
Barbados	19	54,286	< 1	—	—	ND
Bermuda	17	65,441	< 1	0 (2013-2018)	0	0
British Virgin Islands	16	31,196	< 1	—	—	ND
Canada	16	5.85 million	55	1,359 (1992-2013)	61.7	13.8 (+31.4)
Cayman Islands	18	61,559	< 1	—	—	ND
Cuba	16	1.84 million	17	193 (2000-2012)	16	8.5 (–19.4)
Curacao	19	30,593	< 1	—	—	ND
Dominica	22	73,925	< 1	—	—	ND
Dominican Republic	29	3.12 million	29	—	—	ND
Grenada	26	28,034	< 1	—	—	ND
Haiti	33	3.62 million	34	—	—	ND
Puerto Rico	18	598,500	6	—	—	ND
Jamaica	23	664,700	6	36 (1982-2012)	1.8	6.8 (–35.2)
St Kitts and Nevis	20	55,345	< 1	—	—	ND
St Lucia	19	33,980	< 1	—	—	ND
St Martin	26	32,125	< 1	—	—	ND
St Vincent and the Grenadines	24	26,375	< 1	—	—	ND
Trinidad and Tobago	21	287,490	2	11 (2001-2006)	1.8	0.6 (–94.2)
Turks and Caicos Islands	22	35,446	< 1	—	—	ND
United States	19	61.88 million	578	9,709 (1993-2012)	511	12.4 (+18.1)
US Virgin Islands	20	21,453	< 1	—	—	ND
Central America						
Belize	31	116,151	< 1	—	—	ND
Costa Rica	22	1.079 million	10	82 (1993-2012)	4	4.0 (–61.9)
El Salvador	27	1.722 million	16	—	—	ND
Guatemala	35	5.9 million	55	—	—	ND
Honduras	32	2.96 million	28	12 (2002-2012)	1.1	1.6 (–84.8)
Mexico	27	34.88 million	326	36 (1997-2013)	2.25	3.5 (–66.7)
Nicaragua	29	1.8 million	17	—	—	ND
Panama	27	1.106 million	10	—	—	ND
Oceania						
American Samoa	30	55,641	< 1	—	—	ND
Australia	19	4.67 million	44	895 (1992-2014)	38.9	11.6 (+10.5)

(Continued on following page)

TABLE A1. Epidemiologic Characteristics of Neuroblastoma Per Country (Continued)

Oceania						
Fiji	28	253,540	2	—	—	ND
French Polynesia	23	65,091	< 1	—	—	ND
Guam	25	41,057	< 1	—	—	ND
Kiribati	35	40,739	< 1	—	—	ND
Marshall Islands	34	53,127	< 1	—	—	ND
Federated States of Micronesia	33	34,829	< 1	—	—	ND
Nauru	31	13,649	< 1	—	—	ND
New Caledonia	23	64,505	< 1	16 (1990-2013)	0.6	12.9 (+22.9)
New Zealand	20	958,800	9	178 (1993-2012)	9.3	11.3 (+7.6)
Northern Mariana Islands	26	55,144	< 1	—	—	ND
Palau	19	21,729	< 1	—	—	ND
Papua New Guinea	36	2.97 million	28	—	—	ND
Samoa	37	72,682	< 1	—	—	ND
Solomon Islands	39	238,423	2	—	—	ND
Tonga	36	38,887	< 1	—	—	ND
Tuvalu	29	11,192	< 1	—	—	ND
Vanuatu	36	99,447	1	—	—	ND
South America						
Argentina	25	11.06 million	103	164 (1991-2013)	7.5	8.6 (–18.0)
Bolivia	32	3.53 million	33	—	—	ND
Brazil	22	46.04 million	430	134 (1995-2012)	7.9	8.4 (–20)
Chile	20	3.61 million	34	59 (1993-2013)	2.9	4.2 (–60.0)
Colombia	3	11.29 million	105	59 (1992-2003)	5.3	4.0 (–61.9)
Ecuador	28	4.65 million	43	39 (1993-2013)	1.9	1.9 (–81.9)
Guyana	29	225,579	2	—	—	ND
Paraguay	29	1.98 million	18	—	—	ND
Peru	27	8.69 million	81	—	—	ND
Suriname	26	146,484	1	2 (1980-2008)	0.1	0.2 (–98.1)
Uruguay	21	725,970	7	148 (1993-2012)	7.4	11.2 (+6.7)
Venezuela, RB	28	8.95 million	83	—	—	ND

Data adapted.[7,8,10-23]

Abbreviation: ND, no data.

