Reporting Incidences of Neuroblastoma in Various Resource Settings

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Abstract

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
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 Bank7 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      |

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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 |
|--------------------|---------------------------------------------------------------------------------|--------|
| 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

| Country        | AIR/ASR/CIR (percentage of incidence difference from 10.5 cases/million children) | Source |
|----------------|---------------------------------------------------------------------------------|--------|
| 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      |

(Continued on following page)
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).
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).
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.

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

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,
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...
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%. 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. Screening studies only proved to identify more tumors with favorable histology, but not advanced disease, nor did it improve overall survival outcomes. 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. This represents 0.7 cases/million infants screened. 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. Autopsy case series have demonstrated that a variety of neoplasms including cardiac neoplasms and CNS tumors account for the largest number of cases. 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. 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.

| 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.

FIG 3. The number of reported cases of neuroblastoma per year in children under age 15 years.
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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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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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) | Population < 0-14 Years (2017) | Expected No. of Cases (10.5 per million children per year) | 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)                                      | 11.1                          | 11.1 (~5.7)                                   |
| Rwanda            | 40                 | 4.8 million                                           | 45                              | —                                                           | —                             | ND                                            |

(Continued on following page)
| Country                      | Percent of Children 0-14 Years Per Population (2017) | Population < 0-14 Years | 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) |
|------------------------------|-----------------------------------------------------|-------------------------|------------------------------------------------------------|--------------|--------------------------------|-----------------------------------------------|
| Sao Tomé and Príncipe        | 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) | 1.0 (−90.5)                   | ND                                            |
| Zambia                       | 45                                                   | 7.69 million            | 71                                                         | —            | —                              | ND                                            |
| Zimbabwe                     | 41                                                   | 6.77 million            | 63                                                         | 7 (2003-2012) | 0.78 (−86.7)                  | ND                                            |
| Algeria                      | 29                                                   | 11.98 million           | 111                                                        | 112 (1996-2014) | 6.2 (−31.4)                   | 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                                            |

(Continued on following page)
### Table A1. Epidemiologic Characteristics of Neuroblastoma Per Country (Continued)

| Country                        | Population | Incidence Rate | Mortality Rate | Survival Rate | Other Notes |
|--------------------------------|------------|----------------|----------------|---------------|-------------|
| 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  | 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

| Country     | Population    | Incidence Rate | Mortality Rate | Survival Rate | Other Notes |
|-------------|---------------|----------------|----------------|---------------|-------------|
| 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) |

(Continued on following page)
| Country                  | Population | Year Range | Annual Incidence | 5-Year Incidence | 10-Year Incidence |
|--------------------------|------------|------------|------------------|------------------|-------------------|
| Belgium                  | 17         | 1.92 million | 216 (2004-2013) | 11.3             | 13.4 (+27.6)      |
| Bosnia and Herzegovina   | 14         | 490,980    | 4                | —                | —                 |
| Bulgaria                 | 14         | 994,280    | 9                | 178 (1990-2013)  | 7.7              |
| Channel Islands          | 15         | 24,681     | < 1              | —                | —                 |
| Croatia                  | 15         | 623,100    | 6                | 113 (2000-2014)  | 8                |
| Cyprus                   | 17         | 145,316    |                  | 27 (1998-2013)   | 1.8              |
| Czech Republic           | 15         | 1.58 million | 15             | 467 (1990-2012)  | 21.2             |
| Denmark                  | 16         | 919,840    | 9                | 160 (1981-2000)  | 8                |
| Estonia                  | 16         | 1.32 million | 21             | 50 (1990-2012)   | 2.27             |
| Faroe Islands            | 20         | 51,095     | < 1              | —                | —                 |
| Finland                  | 16         | 880,480    | 8                | 26 (1987-2003)   | 1.6              |
| France                   | 18         | 12.09 million | 113           | 1847 (2000-2012) | 142              |
| Germany                  | 13         | 10.76 million | 100            | 2,314 (1996-2012) | 136.1            |
| Gibraltar                | 20         | 34,571     | < 1              | —                | —                 |
| Greece                   | 14         | 1.5 million | 14              | 160 (2009-2016)  | 9.4              |
| Greenland                | 21         | 56,171     | < 1              | —                | —                 |
| Hungary                  | 14         | 1.37 million | 13             | 563 (1991-2014)  | 24.4             |
| Iceland                  | 20         | 67,669     | < 1              | 9 (1990-2014)    | 0.38             |
| Ireland                  | 22         | 1.05 million | 10             | 159 (1994-2012)  | 9.3              |
| Isle of Man              | 16         | 84,287     | < 1              | —                | —                 |
| Italy                    | 14         | 8.48 million | 79              | 142 (1998-2011)  | 10.9             |
| Kosovo                   | 25         | 1.831      | < 1              | —                | —                 |
| Latvia                   | 15         | 292,500    | 3                | —                | —                 |
| Liechtenstein            | 15         | 37,810     | < 1              | —                | —                 |
| Lithuania                | 15         | 427,200    | 4                | 55 (2000-2012)   | 4.2              |
| Luxembourg               | 16         | 94,506     | < 1              | —                | —                 |
| Malta                    | 14         | 64,441     | < 1              | 17 (1995-2015)   | 0.85             |
| Moldova                  | 16         | 568,000    | 5                | —                | —                 |
| Monaco                   | 10         | 38,695     | < 1              | —                | —                 |
| Montenegro               | 18         | 112,044    | 1                | —                | —                 |
| Netherlands              | 16         | 2.73 million | 26             | 436 (1993-2013)  | 20.7             |
| North Macedonia          | 17         | 350,000    | 3                | —                | —                 |
| Norway                   | 18         | 945,000    | 9                | 173 (1990-2013)  | 7.5              |
| Poland                   | 15         | 5.76 million | 53             | 111 (1999-2014)  | 7.4              |
| Portugal                 | 14         | 1.44 million | 13             | 227 (1990-2010)  | 11.35            |
| Romania                  | 15         | 2.95 million | 27             | 25 (2008-2012)   | 6.25             |
| San Marino               | 15         | 33,400     | < 1              | —                | —                 |
| Serbia                   | 16         | 1.12 million | 10.5            | —                | —                 |
| Slovak Republic          | 15         | 815,250    | 7                | 122 (2000-2012)  | 9.3              |
| Slovenia                 | 15         | 309,900    | 3                | 57 (1990-2013)   | 2.1              |
| Spain                    | 15         | 6.98 million | 65             | 1,011 (1990-2013) | 42.1            |
| Sweden                   | 18         | 1.8 million | 16              | 291 (1990-2011)  | 13.2             |

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

| Country                        | Years | Population | Cases | Incidence Rate | 95% CI |
|-------------------------------|-------|------------|-------|----------------|--------|
| **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)
| Country                        | Population       | Cases | Incidence 2015 | Incidence 2016 | Rate 2015 | Rate 2016 | Change Rate 2015–2016 |
|-------------------------------|------------------|-------|----------------|----------------|-----------|-----------|-----------------------|
| **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 | 105 (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.