Childhood Neuroblastoma: Incidence and Survival in Argentina. Report from the National Pediatric Cancer Registry, ROHA Network 2000–2012

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Background. There are reports indicating a low incidence of neuroblastoma (NB) in some developing countries but no conclusive data are available from population-based studies at a national level. ***Purpose.*** To describe the incidence and survival of 971 patients with NB in Argentina with data from the National Pediatric Cancer Registry (ROHA), and the impact of age, gender, stage, regional, and socioeconomic indicators on outcome. ***Methods.*** All cases of NB reported to ROHA (2000–2012) were the subject of the analysis. Annual-standardized incidence rate (ASR) was calculated using the National Vital Statistics and survival was estimated. The extended human development index (EHDI) was used as the socioeconomic indicator. ***Results.*** ASR was 8.3/1,000,000 children (0–14 years) and remained stable along this period. Regional variation in ASR ranged from 3.4 in the Northwest to 9.8 in the Central region, being most marked in the first year of life. Five-year survival rate (SR) was 47%, with no sex difference. For patients older than 18 months, it was 36%, for stage IV 23%, for those born in the Northeast region 38%, and for those with an amplified MYCN 15%. Residents in provinces with a higher EHDI had a better 5-year survival (57% vs. 41% for lower EHDI) and higher ASR (12.3 vs. 5.6 for lower EHDI). Stage and MYCN status showed an independent inferior prognosis. ***Conclusions.*** ASR of NB in Argentina is lower than in developed countries, with considerable regional variation. SRs are also lower than in developed countries. Pediatr Blood Cancer 0000;00:000–000. © 2016 Wiley Periodicals, Inc.

Key words: cancer; children; incidence; neuroblastoma; survival

INTRODUCTION

According to the International Classification of Childhood Cancer (ICCC), neuroblastic tumors belong to a family of neoplasms classified as Group IV, of which ganglioneuroblastoma (GNB) and neuroblastoma (NB) represent 97%.[1] Neuroblastic tumors show a varied biological and clinical behavior ranging from spontaneous regression to progression, and they may either respond to treatment or become resistant to it.[2,3]

NB accounts for 7–10% of childhood cancer in the United States and most European countries with a standardized incidence rate between 8 and 14 cases per million.[4–7] Differences in terms of incidence were reported in different regions of Europe. These differences were even more pronounced when comparing incidence rates in children under 1 year of age. Racial differences in incidence have been described in the United States and a low incidence rate has been reported in some Latin American countries. This variability shows the complexity of this tumor from the epidemiological point of view and some concerns have emerged regarding its low incidence in developing countries.[8–10]

Data analysis using the classification system developed by an international NB risk group confirms the predictive value of age with a cut-off point at 18 months. Histology is another important variable for prognosis. Biological factors, such as MYCN status and an 11q deletion, are associated with poor prognosis.[11]

According to patient risk status, the treatment includes surgery, chemotherapy, radiotherapy, immunotherapy, and transplantation. In high-risk patients, the treatment is intensive requiring a tertiary care facility.

Argentina is a large country with differences in terms of the sociocultural and economic conditions. The National Pediatric Cancer Registry (ROHA) was created in the late 1990s by the Kaleidos Foundation, adopting standard methods in cancer registry. ROHA has worked together with the Argentine National Cancer Institute under the Ministry of Health since 2010. ROHA coverage is estimated to be 93% of pediatric cancer cases.[12,13] The country has a public health system that coexists with social security and prepaid insurance systems. Regardless of insurance status, 80% of children with cancer are treated at public institutions, the treatment being free of charge. Around 40% of children with cancer migrate to another city to receive the treatment. Nevertheless, due to the significant socioeconomic disparities and constraints in transportation there is still inequality in access to care, especially in the early stages of diagnosis.[13,14] The data of vital statistics in Argentina with information from the ROHA allow for analysis of incidence and survival of children with NB. Since these data include socioeconomic indicators, they allow us to determine the impact on survival in different jurisdictions.

Children with cancer living in developing countries are less likely to survive than children living in developed countries.[15–18] This difference may be due to delayed diagnosis, lack of

Abbreviations: AAPC, average annual percentage change; ASR, annual-standardized incidence rate; DCO, death certificate only; EHDI, extended human development index; GNB, ganglioneuroblastoma; ICCC, International Classification of Childhood Cancer; INSS, International Neuroblastoma Staging System; NB, neuroblastoma; POU, pediatric oncology unit

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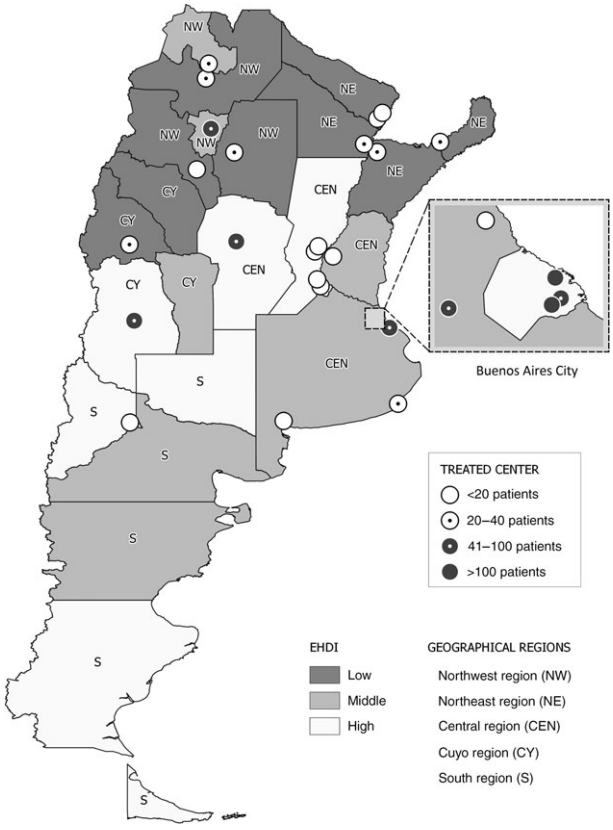

Fig. 1. Map of Argentina. Geographic regions, treating center, and the extended human development index (EHDI) by province. Source: ROHA–National Office of Population Census.

adequate access to healthcare facilities, disparity in the experience of the treating centers (number of new cancer patients per year), and lack of participation in cooperative studies.[19–21]

This article reports the incidence and 5-year survival of children with GNB-NB (ICCC IVa) registered in the ROHA over a period of 13 years. Additionally, we describe the association with sex, age, region of the country, human development index, morphology, stage, number of new cancer patients per year in the treatment center, and MYCN.

MATERIALS AND METHODS

Argentina extends over 2.8 million square kilometers. Its population is mainly urban (90%); 46% of the population is distributed over the Federal District and in the Buenos Aires province. Argentina has 24 political units: 23 provinces and the city of Buenos Aires, the Federal District. Political units are commonly grouped into five major geographical areas ("regions"), as shown on the map (Fig. 1).

The population aged 0–14 years was 10.2 million in 2000, with the following distribution: 60% in the Central region, 14% in the Northwest region, 12% in the Northeast region, 8% in the region of Cuyo, and 6% in the South region. There are 28 public hospitals that treat children with cancer, performing partial or complete treatments, of which 18 are provincial referral hospitals with different levels of complexity. Three tertiary hospitals serve 50% of cancer patients (each year at the national pediatric hospital more than 400 new oncology patients are seen).

The data provided by the ROHA network come from different sources. Most cases are reported by pediatric oncology unit (POU) located in all regions of the country. In addition, the ROHA obtains information from 10 cancer registries that are not only pediatric. Data from each patient include name, document number, date of birth, sex, site of residence, address, histopathology, tumor site, stage, and the method of diagnostic confirmation (microscopic confirmation, imaging studies, death certificate only [DCO]). The cases are coded according to the third edition of the International Classification of Diseases for Oncology (ICD-O3) and the ICCC-3.[1,22]

Population data were obtained from the National Office of Population Census (INDEC). The cases themselves were identified from the ROHA. A case was defined as a child younger than 15 years diagnosed with NB between January 1, 2000 and December 31, 2012, and living in Argentina at the time of such diagnosis. Factors considered in the analysis included gender, age at diagnosis, tumor stage according to the International Neuroblastoma Staging System (INSS), MYCN status, geographic region, hospital category treating the cancer according to the annual volume of patients (less than 20; 21–40; 41–100; more than 100), and socioeconomic indicator of the province where the child was living at the time of diagnosis. The expanded human development index (EHDI) of each province in 2006 was used as a socioeconomic indicator. Specifically, the EHDI provides information on the status of each jurisdiction as related to the possibility of leading a long and healthy life (life expectancy and infant mortality from preventable causes), education (literacy rate and quality of education rate), and decent standard of living (total family income per capita, employment rate, and unemployment rate). Based on their EHDI, provinces were classified into three groups: high (above 0.768), medium (between 0.752 and 0.703), and low (below 0.700). The average EHDI of the country was 0.704; eight provinces had a high EHDI, seven had a medium EHDI, and nine had a low EHDI (Fig. 1).[23] The discrepancy existing between the level of development and access to tertiary centers in the capital city in the same province complicates comparison with the situation in other provinces with a similar EHDI.

STATISTICAL ANALYSIS

The numerical variables were summarized using medians and 25th and 75th percentiles; categorical variables are presented as counts and percentages. Incidence and mortality rates were calculated using Epidat (version 3.0).[24] Standardized incidence rates are presented by age (annual-standardized incidence rate [ASR]), using the world standard population and expressed per million children under 15 years.[25]

The program "joinpoint regression" from the National Cancer Institute of the United States evaluates whether the observed trend of changes in standardized incidence rates used is statistically significant. The estimated average annual percent change (AAPC), representing the percentage increase or decrease in average ASR, was analyzed.[26] IBM SPSS Statistics, Version 21.0 (IBM Corp., 2012) was used for survival analysis.[27] Probabilities of survival at 5 years were estimated using the actuarial method.[28] The endpoint of the study was time of death from

TABLE I. Incidence Rate of Neuroblastoma (ICCC IV(a)) in Argentina, 2000–2012 (Source ROHA)

Neuroblastoma	Cases	ASR[a]	95% CI
Country	971	8.3	7.7–8.8
By sex			
Female	462	8.0	7.3–8.8
Male	509	8.6	7.8–9.3
By age			
<1	295	32.9	22.4–50.4
1–4	507	14.6	10.8–20.1
5–9	125	2.8	1.6–5.4
10–14	44	1.0	0.3–2.5
By region			
Central—EHDI: 0.774	710	9.8	9.0–10.5
Northeast—EHDI: 0.653	72	5.7	4.4–7.0
Northwest—EHDI: 0.673	51	3.4	2.4–4.3
South—EHDI: 0.787	64	6.7	6.6–10.8
Cuyo—EHDI: 0.718	74	7.4	5.7–9.1
By EHDI			
Low	128	5.6	4.6–6.6
Middle	207	7.2	6.2–8.1
High	249	12.3	10.8–13.9

[a]Age standardized rate per 1,000,000 population aged 0–14 years. CI, confidence interval; EHDI, extended human develop index.

any cause. Overall survival time was calculated as the time from date of diagnosis to date of death, if deceased by 60 months. Otherwise, observations were censored at 60 months. Patients who lost contact with the treating center were classified as lost to follow-up at the date of last contact. Following usual registry conventions, the incidence date was defined as the date of histological confirmation. For cases identified through DCO, the incidence date was defined as the date of death.

The number of cases excluded for lack of monitoring information (10%; n = 101; NB: 90, GNB: 11; Female: 52, male: 49; central region: 95, south region: 2, Cuyo region: 4; high EHDI: 46, middle EHDI: 52, low EHDI: 3). The cases being identified through death certificates were considered in the 5-year survival analysis. Cox regression univariate models were carried out to evaluate the association between the risk of death and the following variables: morphology, sex, age risk group, stage, geographic region, treating center, human develop index, and NMYC status. A multivariate Cox regression model was performed using the variables that were significant predictors of mortality in the univariate models (all except geographic region). The hazard ratio and 95% CI were calculated as appropriate.

RESULTS

A total of 16,808 children aged 0–14 years diagnosed with cancer were reported to the ROHA between 2000 and 2012 (average: 1,293 cases per year). Over this 13-year period, a total of 971 cases were IV(a) ICCC group (6%): 843 patients had NB and 128 patients had GNB, with a median age of 2.2 and 4.5 years, and 5-year survival of 42% and 84%, respectively. Of all IV(a) ICCC-group patients, for 90% (n = 870) data were available for assessment of survival. Diagnosis was confirmed by histology in 96.5% (n = 937) of cases, and by DCO in 3.5% (n = 34). Over the study period, 46% of all patients were treated at hospitals located in their province of residence. Of all patients that migrated to get treatment, 85% went to Buenos Aires City and 15% to hospitals located neither in the province of residence nor in Buenos Aires City. Seventy percent of patients from the province of Buenos Aires (medium EHDI) migrate to be treated in the Capital City (high EHDI).

The age-standardized incidence rate of NB was 8.3/million per year for the period 2000–2012 and did not increase significantly over the time with an AAPC of 1.2%, $P = 0.4$. Incidence rate in males 8.6 (7.8–9.3) was slightly higher than in females 8.0 (7.3–8.8). The incidence rate by age groups is shown in Table I. It was highest in the first year of life, declined thereafter, and cases became rare after the age of 10. The regional variation in ASR was considerable, ranging from 3.4 (2.4–4.3) in the Northwest to 9.8 (9.0–10.5) in the Northeast, a variation that was most marked in the first year of life with a specific age incidence of 49.6 in the South region and 13 in the Northwest (Table II).

A high socioeconomic indicator was associated with a high incidence of 12.3 (10.8–13.9), while incidence declined to 5.6 (4.6–6.6) in the areas with a low socioeconomic indicator (Table I).

MYCN was performed in 48% (n = 475) of 971 patients with NB-GNB (2000: 40%; 2012: 68%) and found to be positive in 91 cases (19%). MYCN was performed in 53% (n = 443) of 843 patients with NB (2000: 43;2012: 72%) and was found to be positive in 90 cases (20%).

In 48% (n = 468) of 971 patients with NB-GNB, the INSS stage was determined; 59 patients (6%) were in stage I, 44 patients (4%) were in stage II, 59 patients (6%) were in stage III, 258 patients (27%) were in stage IV, 48 patients (5%) were in stage IVs, and the stage was unknown in 503 patients (52%). National overall 5-year survival was 47% (95% CI 43–50), with no sex differences.

Table III describes cases that could be assessed for 5-year survival probability, deaths, gender, age groups (<18 month→ 18 month), INSS stage, region (presented in Fig. 1), treating center, EHDI, and MYCN status. Children aged <18 months had the highest survival rate (SR), whereas older children had

TABLE II. Incidence Rate and Survival of Neuroblastoma (ICCC IV(a)) in Argentina, 2000–2012 by Age Groups by Regions (Source ROHA)

	Argentina 2000–2012, n = 971	Central region, n = 704	Northeast region, n = 72	Northwest region, n = 51	Cuyo region, n = 74	South region, n = 64
Age[a]						
0–14	8.3	9.8	5.7	3.4	7.4	8.7
<1	32.9	37.4	19.1	13	34.8	49.6
1–4	14.6	17.8	10.4	6.1	11.4	12.7
5–9	2.8	3.3	2.2	1.4	2.8	2.2
10–14	1.0	1.1	1.1	0.2	1.1	0.7
%Survival at 5 years (95% CI)	47 (43–50)	48 (43–52)	38 (25–51)	43 (28–59)	46 (33–60)	52 (37–66)

[a]Age standardized rate per 1,000,000 population. CI, confidence interval.

the lowest. The lowest 5-year survival was observed in patients at stage IV 23% (95% CI 18–29) and those with an amplified MYCN 15% (95% CI 0.6–22). The Central and South regions had the highest estimated 5-year probability of survival 48% (95% CI 43–52) and 52% (95% CI 37–66), respectively, while the Northeast region had the lowest SR of 38% (95% CI 25–51). SRs below 41% were found in those areas with a low EHDI. Cox regression multivariate model indicated that stage and MYCN amplification status were independent variables associated with risk.

DISCUSSION

The present study shows that there are differences in the incidence and SRs of patients with NB in Argentina compared with both developed and developing countries. Variations between countries, race, and regions have previously been described.[4,6,7] Table IV lists incidence and SRs in Argentina alongside with those reported by selected cancer registries in Latin America, Europe, and the United States.[5,7,9,10] Incidence is higher in Europe and the United States than in Argentina, Uruguay, Chile, Mexico, and Brazil. These regional variations in ASR are considerable, ranging from 13.7 cases per million in Germany to 3.8 cases per million in Mexico.

The same phenomenon we observed in Argentina regions (Fig. 1; Table II) with variation in ASR ranging from 9.8 (9.0–10.5) cases per million in the Central region to 3.4 (2.4–4.3) cases per million in the Northwest region. The incidence rate of NB for regions with a high EHDI was 12.3 (10.8–13.9) while it was 5.6 (4.6–6.6) for those with a low EHDI. (Table I) Thus, patients with NB were less frequent in areas with lower development indicators. Interregional ASR variation was most marked in infants; this group has a different behavior when compared to older patients, having a better prognosis and at the same time more often undergoing spontaneous regression. Difference in cancer incidence rate between developed countries and developing countries has been documented for pediatric cancer as a whole and for specific neoplasms including lymphoma (Burkitt and Hodgkin), adrenocortical carcinoma, retinoblastoma, NB, and acute lymphoblastic leukemia.[10,29] There are several possible explanations for the lower incidence of NB in developing countries, particularly in the first 2 years of life. The population cancer registries vary in quality in low-income countries and one problem is underreporting. In some patients with low-risk NB, the lesion is treated only with surgery and they are never seen at a POU, centers that usually are sources of cancer registries.[29] Differences in insurance policies and access to health care may have an impact on NB incidence data, and the chance of an incidental diagnosis is especially high when diagnostic ultrasound is used frequently.[7] Access to health centers in some regions in Argentina is limited due to inadequate public transport systems and extreme climate conditions. This may be particularly important in the prediagnosis period in patients with NB as suggested by a population study on retinoblastoma.[13]

This study shows no increasing trend of ASR in NB and will serve to establish a starting point for future analysis, AAPC: 1.2% ($P = 0.4$). Reports from Europe as a whole describe that the incidence increased significantly ($P = 0.0001$) from 1978 to 1997, with an AAPC of 1.5 per year until the beginning of the new millennium, for periods that did not overlap with the activity of the ROHA.[7]

Ethnic differences in NB incidence have been described. The rate in some African countries, southern Asia, including India, and black children in the United States was lower than that in Europe and white children.[7] Ethnical factors are difficult to assess in Argentina where the population is composed of a mixture of native and European and Asian immigrants. Registries may consider collecting this information to obtain relevant data from their particular background.

Five-year survival for patients with NB in Argentina was 47% (95% CI 43–50), lower than that reported for more developed regions. Table IV presents main survival estimates for Argentina, Germany, the United States, Europe as a whole, Uruguay, Chile, Brazil, and Mexico. Although in Argentina survival is lower, survival patterns are quite similar to those reported for high-income countries. Survival gaps between high- and middle/low-income countries are not unexpected.[20] The low survival observed in this study may in part be explained by the much lower incidence in younger children (better prognosis), compared with the incidence rate in younger children in high-income countries. (Table IV) Information on stage at diagnosis and MYCN status is important when describing the survival of children with NB-GNB: Overall, 48% (n = 468) had an INSS stratification and 48% had a MYCN status. Rice et al. [30] recommend to include MYCN status for patients with NB in national cancer registries.

TABLE III. Five Years Survival Probabilities of Neuroblastoma (ICCC IV(a)) in Argentina, 2000–2012 by Sex, Age Group, Stage, Region, Treated Center, Extended Human Develop Index, and by MYCN (Source ROHA)

				Univariate model		Multivariate model		
Neuroblastoma	Cases	Deaths	Percentage	Hazard Ratio (95% CI)	*P*-value	Hazard Ratio (95% CI)	*P*-value	Survival 5 years Prob (%) (95% CI)
Morphology					<0.001		<0.001	
Neuroblastoma	753	355	47	1		1		42 (38–46)
Ganglioneuroblastoma	117	13	11	0.2 (0.1–0.3)	<0.001	0.2 (0.1–0.3)		84 (75–92)
By sex					0.05		0.3	
Female	410	160	39	1		1		50 (44–55)
Male	460	208	45	1.2 (1.0–1.5)	0.05	1 (0.9–1.3)		45 (40–50)
By age risk group					<0.001		0.07	
0–18 months	387	107	28	1		1		63 (57–69)
>18 months	483	261	54	1.7 (1.4–2.1)	0.001	1.4 (1.1–1.8)		36 (30–40)
By stage					<0.001		<0.001	
I	57	3	5	1		1		92 (84–100)
II	41	5	12	2.7 (0.6–1.0)	0.23	2 (0.5–8.3)	0.35	83 (69–97)
III	59	21	36	7.8 (2.3–26.1)	0.001	6.3 (1.8–21)	0.003	55 (40–70)
IV	253	178	70	14.6 (4.6–45.8)	<0.001	8.4 (2.6–27)	<0.001	23 (18–29)
IVs	46	14	30	8.5 (2.4–29.5)	0.001	6.5 (1.8–23)	0.004	61 (45–78)
Missing	414	147	36	7.8 (2.5–24.4)	<0.001	6.2 (1.9–20)	0.02	52 (47–58)
By region					0.605			
Central	615	256	42	1				48 (43–52)
Northeast	72	35	49	1.2 (0.9–1.8)	0.213	–	–	38 (25–51)
Northwest	51	23	45	1.1 (0.7–1.7)	0.575	–	–	43 (28–59)
South	62	24	39	1.2 (0.8–1.8)	0.383	–	–	52 (37–66)
Cuyo	70	30	43	1.1 (0.8–1.7)	0.495	–	–	46 (33–60)
Treated center					<0.001		0.001	
>100	315	126	40	1		1		52 (45–58)
<20	136	42	31	0.8 (0.5–1.1)	0.16	0.9 (0.6–1.3)	0.64	59 (49–69)
20–40	121	56	46	1.4 (1.0–1.9)	0.04	1.2 (0.8–1.6)	0.31	40 (30–50)
41–100	217	96	44	1.1 (0.8–1.4)	0.70	1 (0.7–1.3)	0.93	44 (36–51)
Missing	81	48	59	2.1 (1.5–2.9)	<0.001	2.1 (1.4–3.1)	<0.001	27 (16–38)
By EHDI							0.012	
High	203	67	33	1		1		57 (49–65)
Middle	536	239	45	1.4 (1.0–1.8)	0.02	1.6 (1.2–2.1)	0.003	48 (40–49)
Low	131	62	47	1.5 (1.0–2.1)	0.01	1.7 (1.1–2.4)	0.009	41 (31–50)
By MYCN					<0.001		<0.001	
Negative	320	89	28	1		1		63 (57–70)
Positive	82	64	78	3.4 (2.4–4.7)	<0.001	2.5 (1.8–3.5)	<0.001	15 (0.6–22)
Missing	468	215	46	2.0 (1.6–2.6)	<0.001	1.8 (1.4–2.4)	<0.001	43 (38–48)

CI, confidence interval. EHDI, extended human develop index.

The ROHA has collected this information since the beginning and improved coverage from 43% in 2000 to 72% in 2012 because of the commitment of oncologists who are part of the ROHA network. In the multivariate analysis, the current study found that MYCN amplification status and stage were independent variables showing the net survival (Table III). Our study also provides data on the influence of the center on the outcome of children with NB. Current treatments of high-risk patients with NB are complex and therefore few centers in developing countries are able to provide adequate therapy. Survival at a center seeing more than 100 oncology patients yearly was 52% (95% CI 45–58), while at a center seeing 20–40 patients yearly survival was 40% (95% CI 30–50). (Table III) The treatment of children with cancer at high case volume clinics and specialized hospitals leads to improved outcome.[19] Defining referral pathways that prioritize early transfer of high-risk patients to these specialized centers may increase survival chances. In high-income countries, 5-year survival in pediatric cancer has improved from 30% in the 1960 to 80% in the 2000, a progression that was made possible by collaboration among pediatric oncologists who were able to implement clinical trials.[31] The International NB Risk Group and the Children Oncology Group were very important for a better understanding of the tumor biology and the improvement of treatment for patient survival.[32,33] The present study has several limitations. First, the data were provided by a national population registry that may result in some underreporting of cases; second, staging and MYCN status were not available for all cases; and third, there is lack of data on the ethnic background of the patients.

TABLE IV. Incidence Rate of Neuroblastoma (ICCC IV(a)) per Million 2000–2012 by age groups in Argentina, Alemania, the United States, Europa, Uruguay, Chile, Mexico and Brazil (Source ROHA)

	Argentina 2000–2012, n = 971	Germany[5] 2004–2013, n = 1,236	United States[6] 2007–2011	Europe[7]	Uruguay[29] 2001–2010, n = 69	Chile[30] 2007–2012, n = 88	Mexico[9] 1996–2005, n = 72	Brazil[10] 1998–2002, n = 372
Incidence[a]	8.3	13.7	10.4	10.9	9.1	4.7	3.8	5.9
Under 1 year	32.9	80.4	51.0	52.6	63.1	21.9	18.5	15.3
1–4 Years	14.6	19.8	20.9	18.1	18.1	6.7	5.4	12.4
5–9 Years	2.8	2.9	4.3	2.8	2.3	2.1	1.1	3.8
10–14 Years	1.0	0.7	1.2	1.0	0	0.3	0.2	1.3
Survival at 5 years	47	79	78.6	70.6	57		64	
EHDI[23]	0.775	0.885	0.902	0.702[b]	0.765	0.783	0.750	0.699

[a]Age standardized rate per 1,000,000 population aged 0–14 years; [b]Europe and Asia: Source: http://hdr.undp.org/sites/default/files/hdr_2010_es_summary.pdf. [29]Oral Communication 8/2015. Registro Nacional de Cáncer. Comisión Honoraria de lucha contra el cáncer. Uruguay Barrios E, Garau M, Alonso R, Musetti C. [30]Personal Communication 8/2015. Registro Nacional de Cancer Infantil, Departamento de Epidemiologia, Ministerio de Salud, Chile. Vallebuona Stagno C. EHDI, Extended Human Development Index.

CONCLUSIONS

ASR of NB in Argentina is lower than in developed countries, with considerable regional variation. SRs are also lower than developed countries, partly because of the low incidence of cases in infants with better prognosis. Improving these results remains a challenge for our health care system.

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