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Neural tube defects in Latin America and the impact of fortification: a literature review

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Abstract

Objective—Data on the prevalence of birth defects and neural tube defects (NTD) in Latin America are limited. The present review summarizes NTD prevalence and time trends in Latin American countries and compares pre- and post-fortification periods to assess the impact of folic acid fortification in these countries.

Design—We carried out a literature review of studies and institutional reports published between 1990 and 2010 that contained information on NTD prevalence in Latin America.

Results—NTD prevalence in Latin American countries varied from 0.2 to 9.6 per 1000 live births and was influenced by methods of ascertainment. Time trends from Bogota, Costa Rica, Dominican Republic, Guatemala City, México and Puerto Rico showed average annual declines of 2.5% to 21.8%. Pre- and post-fortification comparisons were available for Argentina, Brazil, Chile, Costa Rica, Puerto Rico and México. The aggregate percentage decline in NTD prevalence ranged from 33% to 59%.

Conclusions—The present publication is the first to review data on time trends and the impact of folic acid fortification on NTD prevalence in Latin America. Reported NTD prevalence varied markedly by geographic region and in some areas of Latin America was among the lowest in the world, while in other areas it was among the highest. For countries with available information, time trends showed significant declines in NTD prevalence and these declines were greater in countries where folic acid fortification of staples reached the majority of the population at risk, such as Chile and Costa Rica.

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Birth defects, including neural tube defects (NTD), are one of the leading causes of infant and neonatal mortality in countries undergoing an epidemiological transition because of declines in infant mortality and improvements in the environment(1). Globally, NTD prevalence is estimated to be over 300 000 new cases per annum, with over 40 000 deaths and 2.3 million disability-adjusted life years (2). Further, in low-income countries, 17% to 70% of neonatal deaths from birth defects are attributed to NTD (3). However, scanty and fragmented surveillance information hinders the ability to adequately determine the prevalence of NTD in more than 11 million births per year in Latin America (4). Birth defects surveillance information is vital for monitoring and evaluating the impact of prevention and intervention programs.

Observational studies reinforce the evidence from clinical trials that have shown conclusively that consumption of staples fortified with folic acid and adequate periconceptional folic acid supplementation reduce the risk of NTD (3,5–7). Currently, all Latin American countries except Venezuela have mandatory fortification legislation and programs aimed at decreasing conditions related to deficiencies of folic acid and other micronutrients. Few countries, however, have established monitoring and evaluation components to assess the impact of their NTD prevention programs and fewer still have identified time trends pre- and post-fortification (8).

The present review had two main objectives: (i) to summarize NTD prevalence and time trend data in Latin American countries; and (ii) to compare pre- and post-fortification periods to assess the impact of folic acid fortification on NTD prevalence in these countries.

Methods

We carried out a review of studies published between 1990 and 2010 to identify reports containing information on NTD prevalence and, when appropriate, the time periods in which fortification programs were initiated. We searched CINAHL, Cochrane Collaboration, EMBASE, Global Health, Google Scholar, Ingenta, Medline, the Pan-American Health Organization search engine, PubMed, Red de Revistas Científicas de America Latina y el Caribe, España y Portugal, Revista Médica de Chile, the Latin American and Caribbean Health Sciences Literature (LILACS) and Web of Science for published information. The review was conducted between March 2007 and December 2010. The titles and abstracts were reviewed to determine if the content was related to NTD prevalence and/or folic acid fortification in the region. Studies identified for potential inclusion were assessed by two of the co-authors.

We considered for inclusion observational studies (cohort, case–control, cross-sectional and ecological studies) that included the following information: a clear description of the study population and methods (case definition and methods of case ascertainment, demographics); diagnosis of NTD in live-born infants in the first year of life and in stillbirths; population setting (clinic, hospital or population derived); number of type-specific cases and/or total cases; prevalence rates or ratios; limitations and biases; and any information regarding folic acid fortification interventions, when available. Studies were scored independently by two of the co-authors based on the following aspects of study quality: (i) clarity of case definition;

(ii) methods of case ascertainment; (iii) reported prevalence rates or ratios; (iv) number of live births; (v) study limitations; and (vi) biases. Each category contributed one point. The scores of each independent reviewer were averaged, and the articles or reports were then classified based on their total score as ‘very good’ (score=5–6), ‘good’ (score=3–4), ‘satisfactory’ (score=2) or ‘poor’ (score=0–1). Only studies classified as good or very good were included in the review.

We excluded publications with fewer than 5000 live births per year; those that did not report the number of cases or reported the NTD prevalence without inclusion of the total number of births; those that reported graphs without point estimates; publications in which the information was based on mortality only; and/or publications that included only one type of NTD (i.e. anencephaly or spina bifida or encephalocele). Publications containing total NTD cases only were included when the methodology specifically defined at least two forms of NTD.

Most of the publications on NTD used data from national or regional registries and surveillance/vital statistics systems. The registries cited most often were the Latin American Collaborative Study of Congenital Malformations (ECLAMC) (9), the Costa Rica Congenital Malformations Registry (CARCM)(10), the Cuban Congenital Malformations Registry (RECUMAC)(11), the Mexican External Malformations Epidemiological Surveillance Registry (RYVEMCE)(12) and the Puerto Rico Congenital Malformations Surveillance Systems(13). In addition, reports from Argentina, Brazil and México also used data sources based on national or local hospital discharge data (14–16). Additionally, we included information from institutional reports published by the Universidad de San Carlos in Guatemala, the Costa Rica Ministry of Health, the Dominican Republic Ministry of Health and the Fundación de Niños Saludables in Honduras.

Analysis

To increase stability of the NTD prevalence estimates, we grouped years of reported cases and births when possible. Time trends were estimated from those publications that provided at least four time points. We present basic trends in prevalence by computing prevalences (with 95% confidence intervals) of NTD over time within source using exact Poisson limits (17,18). We analyzed basic time trends using Poisson and negative binomial distribution models for each source separately:

$$\log(\text{NTD}) \approx \text{intercept} + \beta * \text{year} + \log(\text{LB}),$$

where NTD is the case count and LB is the live birth count. Results of the model provided a summary of temporal trends as prevalence ratios, expressed as relative changes in prevalence per unit changes in time.

The impact of fortification was evaluated by comparing prevalences before and after the onset of fortification. The most basic comparison was the calculation of a single prevalence rate ratio (PRR)(19,20), with approximate limits for 95% confidence:

$$PRR_{Trend} = \text{Prevalence}_{Post} / \text{Prevalence}_{Pre}.$$

For countries with sufficient data for both pre- and post-fortification periods, we used a more complex model:

$$\text{Log(NTD)} \approx \text{intercept} + \beta_{\text{fort}} \times \text{fort} + \beta_{\text{year}} \times \text{year} + \beta_{\text{fort} \times \text{year}} \times \text{fort} \times \text{year} + \text{log(LB)},$$

whose term $\beta_{\text{fort} \times \text{year}}$ gives a basis for a test of change in trend across fortification. Additionally, judicious use of the β_{fort} and β_{year} terms allowed estimation of trends for both pre- and post-fortification periods. SAS GENMOD version 9.2 software was used to produce all estimations and standard errors (21).

Results

Search results

The search identified a total of 2457 citations published from January 1990 to December 2010. Of these, 2295 were excluded because they duplicated data from original reports or were commentaries on previously published data. Of the remaining 162 citations, thirty three were excluded because reports could not be located after extensive library and electronic searches as well as three or more unsuccessful attempts to contact the authors. Another sixty-five were excluded after reading the abstract and/or full text because the reports did not include specific NTD information, included only one type of NTD, or had a denominator of less than 5000 live births. This process identified a total of sixty-four reports. In addition, we included data from five institutional reports, two of which were published by the Universidad de San Carlos in Guatemala and one each by the Costa Rica Ministry of Health, the Dominican Republic Ministry of Health and the Proyecto Niños Saludables in Honduras. Of the sixty-nine reports that satisfied the inclusion criteria, fifty-one (73.9%) were published in peer-reviewed journals. Table 1 summarizes the studies included in the present review by country, study design, time period covered, data sources, number of NTD cases by type and total, number of live births, and prevalence of NTD per 1000 live births by type and total.

Reports were available from fifteen countries and one sub-region. Information was not available for Bolivia, El Salvador, Nicaragua and Panama, and although Paraguay reported NTD prevalence, its birth cohort was too small to satisfy our inclusion criteria.

Within each country, the data, which covered single or multiple locations and different time periods and hospitals, varied by methodology used and geographic areas covered. Data for most countries covered regional and/or local areas; however, data for Argentina, Costa Rica, Cuba and Puerto Rico were also collected at the national level. ECLAMC reported NTD prevalence for South America and several locations in the subcontinent. In a majority of reports, spina bifida cases were the largest contributor to total NTD cases.

Among the sixty-nine reports, forty-two (60.9%) were based on hospital registries (structured case definition and inclusion criteria), fourteen (20.3%) on review of medical records, seven (10.1%) on hospital discharge data and the remaining six (8.7%) were based on population-based registries, review of hospital delivery logs or reports from live birth surveillance systems. Costa Rica, Cuba and Puerto Rico also included reports from specialty clinics to capture post-discharge diagnoses. In addition, data from Cuba included pregnancy terminations.

Prevalence of neural tube defects

Reported NTD prevalence by country or location (Table 1) showed wide geographic variation within and between countries, ranging from 0.2 to 9.6 per 1000 live births.

National prevalence estimates

National NTD prevalence estimates were available for seven countries: Argentina, Costa Rica, Cuba, Ecuador, Guatemala, México and Puerto Rico. These estimates varied by country and methodology. National registry data showed that NTD prevalence per 1000 live births was 0.45 in Costa Rica (2007)(22), 1.10 in Cuba (2005–2006)(23), 0.82 in Ecuador (2001–2005)(24) and 0.90 in Puerto Rico (2008)(25). National hospital discharge data showed an NTD prevalence of 1.62 in Argentina (2005)(15) and 0.47 in México (2004)(26). NTD prevalence based on national hospital delivery logs was 2.82 in Guatemala (2001–2003)(27).

Regional and local prevalence estimates

Hospital-based registry data have been used to estimate NTD prevalence in specific locations in different countries. For example, Argentina hospital registry data from fifty-nine hospitals in seven regions showed an NTD prevalence of 1.99 per 1000 live births for the period 1994–2007(28). This prevalence is consistent with another hospital registry study in forty-one Argentinean hospitals, which showed that the prevalence of NTD for 1982–2007 was 2.01 per 1000(29). Available hospital registry data from Chile in 1998–2000 showed a similar prevalence. However, NTD prevalence estimates based on hospital registry data varied within and between locations in Brazil, Colombia, Cuba, México, Uruguay and Venezuela. For example, Brazilian hospital registry data from nineteen ECLAMC-participating hospitals for the periods 2003–2005 and 2005–2007 showed that NTD prevalence was 4.51 and 3.80 per 1000, respectively (29). This NTD prevalence was almost half the 9.60/1000 prevalence reported from Porto Alegre for the time period 2000–2005(30). In contrast, NTD prevalence in hospital registry data from Minas Gerais and Sao Paulo for comparable time periods ranged from 1.13 to 4.87 per 1000 live births (16,31).

Variations in NTD prevalence estimates were also observed between hospital delivery logs and hospital records data in several locations. For example, hospital delivery log data from two Guatemala City hospitals in 2004–2008 showed an NTD prevalence of 2.00 per 1000 live births(32), compared with 3.47 per 1000 in 2004–2005 identified in data derived from hospital records at the same hospitals (33).

Time trends in prevalence of neural tube defects

Information to assess NTD prevalence time trends was available for Bogota (Colombia), Costa Rica, Cuba, Dominican Republic, Guatemala City (Guatemala), México (RYVEMCE) and Puerto Rico. Overall time trends of NTD prevalence exhibited average annual declines ranging from 2.5% to 21.8 % (Table 2), with the exception of Cuba, which showed an increase; however, it was not possible to model the trend prevalence because the Cuban surveillance system changed its inclusion criteria for the period 2000–2004.

Fortification

All Latin American countries have mandatory folic acid fortification of wheat flour except Venezuela (Table 3). Fortification levels range from 0.35mg/kg to 3.3mg/kg. While most countries started fortification in the late 1990s, Argentina, Brazil, Peru and Uruguay introduced fortification regulation in 2002, 2002, 2004 and 2006, respectively (34–37). In addition, México also fortifies corn flour and Costa Rica also fortifies corn flour, rice and milk (34,38).

Argentina, Brazil, Chile, Costa Rica, Cuba, Puerto Rico and México were the only countries for which information was available to perform a meaningful comparison of changes in pre- and post-fortification NTD prevalence. We directly compared NTD prevalence between these periods by computing NTD prevalence for years pooled pre and post-fortification, summarizing effects as a prevalence ratio with 95% confidence limits. Table 4 depicts the post-fortification changes in NTD prevalence and their corresponding PRR and 95% CI for Argentina, Brazil, Chile, Costa Rica, Cuba, México (RYVEMCE) and Puerto Rico. All sites showed significant declines in NTD prevalence ranging from 33.0% to 59.0%. In the case of Costa Rica we were able to fit a more complex model including an interaction term to assess whether the NTD secular trend changed after fortification. Our model yielded a statistically significant interaction term ($P < 0.03$) suggesting that NTD prevalence changed significantly following fortification. The pre-fortification prevalence was estimated at 1% decline (95% CI 24%, 13%) per year, and the post-fortification trend was estimated at 6% decline (95% CI 210.2%, 2.1%) per year.

Discussion

To our knowledge, the present publication is the first one that reviews data on NTD prevalence in Latin America, including time trends and the impact of folic acid fortification. The majority of countries showed a generalized decrease in the NTD prevalence in time, similar to time trend declines previously reported elsewhere (39–41).

Our review showed that fifteen countries reported local and/or regional NTD prevalence and seven of them reported, in addition, national prevalence of NTD. Comparisons of NTD prevalence between and within countries showed regional and/or local differences, most probably due to variations in data collection methods. In our review, the main data collection methods used to estimate NTD prevalence were hospital-based registries, clinical examination at birth and review of hospital records, hospital discharge data, hospital delivery logs and live birth statistics. Hospital-based registries have defined inclusion and

exclusion criteria and clear diagnostic criteria including specific definitions for case ascertainment and information recording. Hospital clinical examinations at birth can be as effective as hospital registries in recording numbers and types of NTD, if there are in place specific protocols for diagnostic criteria, case inclusion and exclusion, and case ascertainment. However, hospital clinical examinations without specific protocols are more susceptible to biases than registries or structured surveillance systems because these examinations are not standardized and clinicians have differences in case definition, differences in how newborns are examined and differences in how results are recorded. Similarly, hospital discharge data are more susceptible to biases due to differences in criteria within and across hospitals and physicians related to case ascertainment, case recording and ICD (International Classification of Diseases) code assignment in the discharge diagnosis fields. Also, hospital discharge data are susceptible to including multiple records of the same individual and hospital transfers or readmissions, and might contain records of patients who do not belong to the hospital catchment area. In addition to being susceptible to differences in hospitals and medical practices, hospital delivery logs are limited because they do not include cause-specific morbidity or mortality. In addition, NTD are serious defects with a very high mortality and it is essential to count stillbirths when estimating the prevalence of NTD to avoid an underestimation of prevalence.

In summary, hospital-based data, although readily available in many countries, also reflect variations in access to and utilization of health services. The impact of different data collection methods and sources of information on NTD prevalence estimates has been reported previously (42–46).

Differences in NTD prevalence by country can also be explained by geographic variation. For example, higher NTD prevalence in some areas of Brazil, Guatemala, Honduras and México is consistent with higher levels of poverty, higher conception rates for younger mothers, and less access to health services and fortified staples(47,48). In contrast, the observed increase in Cuba's NTD prevalence trend was most likely due to differential ascertainment: changes in inclusion criteria, increase in number of participating hospitals and inclusion of pregnancy terminations (49).

Nevertheless, despite data limitations and geographic variation, these data are important because they can show changes over time.

Fortification

Comparisons between pre- and post-fortification prevalence of NTD showed that fortification efforts were effective in reducing NTD prevalence in Argentina, Bogota (Colombia), Chile, Costa Rica, Guatemala City (Guatemala), México (RYVEMCE) and Puerto Rico. This confirms the reduction in NTD prevalence reported elsewhere after fortification with folic acid (41,50–55) and the previous declines in NTD prevalence reported in the region (29,52,53).

A declining secular trend that started before the implementation of fortification .programs may obscure assessment of the NTD prevention effect of these .programs. Previous publications have reported techniques that include methodological approaches to assess the

potential effects attributable to fortification when a previous declining trend has been identified (56). Using a methodology similar to that reported by Chen et al. (56) we attempted to determine the pre- and post-fortification slopes that represented summaries of the annual NTD prevalence before and after implementation of fortification. However, the only data set in which we could evaluate such changes was from Costa Rica because we had enough data to assess the pre- and post-fortification trend. For the pre-fortification period the slope of NTD prevalence was not different from zero; however, the post-fortification period showed a significant decline in NTD prevalence. This result re-confirms that the decline in NTD prevalence can be accelerated when countries select staples that are highly consumed by the population and monitor and evaluate the levels of folic acid in fortified staples and the impact of their fortification programs. The present review re-asserts that fortification of staples with folic acid results in up to a 59% decrease in NTD cases that could result in reductions in mortality, morbidity and financial burden associated with these conditions (57,58).

Limitations

There are several limitations that could have a bearing on our findings regarding NTD prevalence in Latin America. The overall quality of the review and its results is dependent on the quality of information of the individual studies. The heterogeneity of case ascertainment and years of study across countries and across surveillance programs affected our ability to pool estimates, make direct comparisons or quantitatively evaluate trends across time or countries. The use of voluntary hospital-based surveillance systems that capture only a proportion of the population at risk is also a potential limitation of the study. The under-representation of rural populations in the reported data from some countries can affect estimates.

Conclusion

The present publication is the first to review and report data on NTD prevalence in Latin America including time trends and the impact of folic acid fortification. The surveillance of NTD in Latin America is currently limited because few countries have established systems to report national and local NTD prevalence. However, when data are available, reported NTD prevalence, which varies by geographic region from 0.2 to 9.6 per 1000 live births, is in some areas of Latin America among the lowest in the world while in others is among the highest. Observed declines in NTD prevalence were largest in countries where folic acid fortification of staples reached the majority of the population at risk, such as Chile and Costa Rica. NTD prevalence among countries in which fortification had been implemented showed declines ranging from 33.0% to 59.0%. It was possible to show that fortification has an impact and was consistent for most countries. Selected registries in the region have become proxies for national surveillance systems, and even though they have limited coverage, they constitute the major source of information regarding NTD prevalence and time trends that allow for the monitoring of disease burden and impact of fortification programs. The need for adequate data is central to a better understanding of the magnitude of the public health impact of NTD in the Latin American region and the assessment of the effectiveness of prevention programs. The implementation of national NTD surveillance programs could help to close this information gap.

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NTD Prevalence in Latin America

Table 1

Location	Site	Author	Reference Number	Year Publication	Design	Year(s) Reported	Source	Neural Tube Defects Cases			Total live births	Anencephaly	Spina bifida	Encephalocele	NTD Prevalence (An,SB,En) per 1,000 LB																									
								Anencephaly	Spina bifida	Encephalocele																														
Argentina		Castilla	59	2003	Hospital registry	1999–2001	20 Hospitals ECLAMC			382					2.41																									
																1999	113	51,123	2.21																					
																2000–2001	269	102,747	2.61																					
																1994–2007	59 Hospitals ECLAMC in 7 regions	Metropolitan			1704	216	847	83	648	239,943	1.03	1.32	0.25	1.99										
																															Pampa	83	123	24	230	163,649	0.51	0.75	0.15	1.41
																																Center	85	130	32	247	107,732	0.79	1.21	0.30
																															Cuyo	35	54	17	106	76,506	0.46	0.71	0.22	1.39
																																Northwest	27	34	9	70	62,539	0.43	0.54	0.14
																															Northeast	153	183	51	387	183,638	0.83	1.00	0.28	2.11
																																Patagonia	10	6	0	16	21,213	0.47	0.28	0.00
Brazil		Lopez-Camelo	30	2010	Hospital registry	1982–2007	41 hospitals ECLAMC			1,643,341	0.59	0.83	2.01	2.45																										
															2002–2004	193,509	0.86	1.27	0.32	2.45																				
															2005–2007	All Hospitals except Salta, Tucuman and Tierra del Fuego	74	439	68	581	181,066	0.41	2.42	0.38	3.21															
																	34	238	20	292	179,928	0.19	1.32	0.11	1.62															
															1999–2003	11 Hospitals ECLAMC				272				83,180				3.27												
																													2003–2005 ¹	115	290	58	463	102,751	1.12	2.82	0.56	4.51		
															2005–2007 ²	Hospital and clinics of UFMG/ ECLAMC				89	16	47	30	353	92,843	0.69	2.79	3.8												
																													64	259	30	353	92,843	0.69	2.79	0.32	4.87			
															Santos Dumont, Minas Gerais		Aguar	17	2003	Hospital registry	1990–2000	Hospital and clinics of UFMG/ ECLAMC			124	0.96	3.32	0.68	4.96											
																														2000–2004	SINASC Surveillance System of Live Births	24	83	17	124	24,964	0.96	3.32	0.68	4.96
2000–2006	SINASC Surveillance System on live Births	108	161,341	88	122,100	0.67																																		
		2005–2006	20	39,241	20	39,241	0.51																																	
Rio de Janeiro		Costa	62	2006	Hospital	1999–2001	10% of births in 47 hospitals	1	7	3	11	9,386	0.11	0.75	0.32	1.17																								

Location	Site	Author	Reference Number	Year Publication	Design	Year(s) Reported	Source	Anencephaly	Spina bifida	Encephalocele	Total live births	Anencephaly Prev. per 1,000 LB	Spina bifida Prev. per 1,000 LB	Encephalocele Prev. per 1,000 LB	NTD Prevalence (An,SB,En) per 1,000 LB
		Ramos	63	2008	Hospital discharge	2000–2004	SINASC Surveillance System on Live Births	111	15		486,824	0.23	0.03		0.26
	Sao Paolo	Ogata	64	1992	Hospital registry	1973–1986	Hospital do Servidor Publico ECLAMC	9	11	6	33,535	0.27	0.33	0.18	0.78
		Montelone	65	1994	Hospital Registry	1982–1985	3 Hospitals ECLAMC	7	3	1	10,218	0.69	0.29	0.10	1.08
		Borelli	66	2005	Hospital Registry	Jan 2004-Oct 2004	5 hospitals				6,887				1.89
	Vale de Parcuha Sao Paolo	Nascimento	32	2008	Hospital Discharge Data	2004	SINASC	14	23	1	33,653	0.42	0.68	0.03	1.13
	Porto Alegre	Guardiola	31	2009	Hospital Registry	2000–2005	Complejo Hospitalar Santa Casa-ECLAMC	123	72	61	256	4.6	2.7	2.29	9.6
Chile	Regions 1,5,6,7,8,10,14,15, Metro	Nazer	67	2001	Hospital Registry	1967–1999	18 hospitals ECLAMC	311	374	91	776	0.72	0.86	0.21	1.79
	Regions I, V, VI, VIII and X	Nazer	68	2002	Hospital Registry	1982–1999	5 hospitals ECLAMC	228	69	276	573	0.79	0.24	0.96	1.99
	Metro Region	Nazer	69	2007	Hospital Registry	1982–1999	14 Hospitals/ECLAMC	107	123	34	266	0.76	0.88	0.24	1.90
	Santiago	Cortes	70	2001	Hospital Registry	2001–2003	8 hospitals	12	14	3	29	0.35	0.41	0.09	0.84
		Herrtrampf	53	2004	Hospital Registry	1999–2004	9 Hospitals ECLAMC	37	47	11	94	0.62	0.76	0.18	1.56
		Herrtrampf	71	2008	Hospital registry	1999–2002	9 Public Health Hospitals	66	101	29	205	0.55	0.84	0.23	1.7
						1999–2000		33	41	14	89	0.37	0.46	0.16	1.01
						2001–2002									1.71
						2001–2002									0.97
		Lopez-Camelo	72	2005	Hospital Registry	1982–1989	10 Hospitals ECLAMC	12	163		175,169	0.64	0.93		1.56
						1990–2000	20 Hospitals ECLAMC	145	165		176,958	0.82	0.93		1.75
						2001–2002	16 Hospitals ECLAMC	36	54		113,268	0.32	0.48		0.79
		Lopez-Camelo	30	2010	Hospital Registry	1998–2000	17 Hospitals ECLAMC	44	71	23	138	0.63	1.02	0.33	1.98
						2001–2003		90	112	44	246	0.37	0.46	0.18	1.01
Colombia	Bogota														
	Cundimarca	Garcia	73	2003	Hospital Registry	Oct-97 to May-98 and July to Nov 2000	Instituto materno Infantil ECLAMC	4	9	2	15	0.70	1.58	0.35	2.64
	Bogota, Manizales and Ubaté	Zarate	74	2008	Hospital registry	2001–2007	7 hospitals-ECLAMC				38				0.79
						2001					2				0.88
						2002					4				0.78
						2003					12				1.14
						2004					7				1.08
						2005					7				0.78
						2006					4				1.20

Location	Site	Author	Reference Number	Year Publication	Design	Year(s) Reported	Source	Neural Tube Defects Cases			Total live births	Anencephaly Prev. per 1,000 LB	Spina bifida Prev. per 1,000 LB	Encephalocele Prev. per 1,000 LB	NTD Prevalence (An,SB,En) per 1,000 LB										
								Anencephaly	Spina bifida	Encephalocele															
Costa Rica	Cali	Monsalve	75	2007	Hospital registry	2004–2005	Hosp. Universitario del Valle-ECLAMC	2	52	7	90	0.38	0.65	0.09	0.39										
																22	6,993	3.15							
	Huita Neiva	National	ICDBS, Umaña	77.78	2006, 2009	Population-Based registry	1987–2005	Neiva Hospital	31	52	7	80,326	0.38	0.65	0.09	0.39									
																	24	35	3	62	81,376	0.29	0.43	0.04	3.15
																	17	55	6	78	83,460	0.2	0.65	0.07	3.46
																	24	51	4	79	81,939	0.29	0.62	0.05	1.83
																	18	45	9	72	81,110	0.22	0.55	0.11	4.34
																	17	16	6	39	80,164	0.21	0.2	0.07	1.5
																	12	38	2	52	79,714	0.15	0.47	0.03	0.76
																	15	40	7	62	80,391	0.18	0.49	0.09	0.93
																	10	42	4	56	80,306	0.12	0.52	0.05	0.96
																	17	49	6	72	79,203	0.21	0.62	0.08	0.89
																	29	57	5	91	78,018	0.37	0.73	0.06	0.49
																	15	45	8	68	76,982	0.19	0.58	0.10	0.65
																	12	31	10	53	78,526	0.15	0.39	0.13	0.77
																	18	29	2	49	78,178	0.23	0.37	0.03	0.7
																	17	29	2	47	76,401	0.22	0.38	0.03	0.62
																	14	20	5	39	71,144	0.19	0.28	0.07	0.61
																	4	28	2	34	72,938	0.05	0.38	0.03	0.55
																	11	24	6	41	72,247	0.12	0.33	0.08	0.47
8	19	4	31	71,548	0.11	0.26	0.06	0.57																	
Cuba	National	ICDBS	23	2008	Population-Based registry	2006–2007	RECUMAC Hospitals	10	21	6	37	0.14	0.29	0.08	0.52										
																7	21	4	32	71,180	0.09	0.29	0.06	0.45	
																15	94	119	191,491	0.08	0.49	0.08	0.62		
																14	66	84	234,691	0.06	0.28	0.06	0.36		
								1	56	60	223,546	0.004	0.25	0.06	0.27										

Location	Site	Author	Reference Number	Year Publication	Design	Year(s) Reported	Source	Neural Tube Defects Cases			Total live births	Anencephaly	Spina bifida	Encephalocele	NTD Prevalence (An,SB,En) per 1,000 LB
								Anencephaly	Spina bifida	Encephalocele	Total	Prev. per 1,000 LB	Prev. per 1,000 LB	Prev. per 1,000 LB	
Dominican Republic						2000–2004		80	90		182	0.34	0.38	0.77	
		ICDBS	24	2008	Hospital registry	2005–2006	RECUMAC Hospitals	98	104	46	225	0.44	0.46	0.20	1.1
		Piñar del Río	79	2001	Hospital registry	1998	Hospital Just Legon	9	13	1	23	0.83	1.2	0.09	2.11
			80	2004	Hospital registry	1994–1998	CGPM Hospital	43	31	6	80	0.83	0.59	0.12	1.54
		Habana City	81	2005	Hospital registry	2000–2002	8 Habana hospitals-RECUMAC				130				1.7
		National	82	2008	Hospital Delivery Logs	2000–2006	6 Hospitals				15	0.30	0.15		0.45
						2000–2001		10	5		15	0.30	0.15		0.45
						2002–2003		22	4		26	0.45	0.08		0.54
Ecuador						2004–2005		10	4	14	66,101	0.15	0.06	0.21	
						2006		0	6	6	21,593	0	0.28	0.28	
						1989	3 Hospitals – San Lorenzo de los Mina, Materno Infantil del instituto Dominicano de Seguros Sociales and Luis E. Aybar REDUMAC	2	9	1	12	0.15	0.97	0.07	1.19
Guatemala						2001–2005	12 Hospitals ECLAMC	21	28	6	55	0.31	0.42	0.09	0.82
						2001–2003	All regional and national hospitals (22 hospitals)								
						2001–2003		45	529	68	642	0.20	2.33	0.30	2.82
						2001		19	187	21	227	0.26	2.51	0.28	3.05
						2002		12	190	35	237	0.16	2.54	0.47	3.16
						2003		14	152	12	178	0.18	1.95	0.15	2.28
						2001–2003	Roosevelt and San Juan de Dios, Guatemala City	13	213	26	252	0.35	0.70	5.70	6.74
						2001		5	70	9	84	0.37	5.16	0.66	6.19
						2002		2	85	14	101	0.18	7.45	1.23	8.86
						2003		6	58	3	67	0.48	4.68	0.24	5.41
						2004–2008	Roosevelt and San Juan de Dios, Guatemala City	40	102	25	167	0.48	1.22	0.30	2.00
						2004		7	13	4	24	0.43	0.8	0.25	1.58
					2005		21	19	0	40	1.28	1.16	0.00	2.44	
					2006		7	32	16	55	0.44	2.01	1.01	3.46	
					2007		2	15	1	18	0.11	0.81	0.05	0.99	
					2008		3	23	4	30	0.19	1.39	0.24	1.82	
					November 2004 to December 2005		Roosevelt and San Juan de Dios, and Social Security Hospitals	33	45	11	91	0.71	0.97	0.24	1.97
					2006		Roosevelt and San Juan de Dios Hospitals	23	28	10	61	1.31	1.59	0.57	3.47

Location	Site	Author	Reference Number	Year Publication	Design	Year(s) Reported	Source	Anencephaly	Spina bifida	Encephalocele	Total live births	Anencephaly Prev. per 1,000 LB	Spina bifida Prev. per 1,000 LB	Encephalocele Prev. per 1,000 LB	NTD Prevalence (An,SB,En) per 1,000 LB
Honduras	National	Milla	84	2003	Hospital Clinical examination	200–2001	All public Hospitals	56	80	7	143	0.95	1.36	0.12	2.43
	Tegucigalpa	Hernandez	85	2001	Hospital records, delivery logs and deaths	1998–2000	Hospital Escuela				41				2.23
		Mutchinick	86	1995	Hospital registry	1978–1987	hospitals RYVEMCE	587	500	106	1,193	1.69	1.58	0.34	3.6
		Mutchinick	87	1990	Hospital registry	1978–1984	Hospitals RYVEMCE	360	249	44	653	1.56	1.08	0.19	2.83
Mexico	ICDBMS		88	2006	Hospital registry	1980–2004	25 hospitals participating in RYVEMCE								
						1980–1984		330	226	60	661	1.81	1.24	0.33	3.63
						1985–1989		350	285	56	734	1.99	1.62	0.32	4.17
						1990–1994		481	458	67	1035	1.66	1.58	0.23	3.57
						1995–1999		294	279	53	637	1.43	1.36	0.26	3.1
						2000–2004		89	106	21	246	0.69	0.62	0.16	1.91
	ICDBMS		89	2008	Hospital registry	2005–2006	25 Hospitals RYVEMCE	20	30	6	56	0.41	0.61	0.12	1.14
	Guajuato	Hernandez	90	1991	Hospital medical records	1989–1990	Hospital 48	11	18	1	30	0.65	1.06	0.06	1.77
	Guadalajara	Alfaro-Alfaro	91	1994	Hospital clinical examination at birth	1988–1993	4 Hospitals metro zone	97	93	11	201	1.3	1.25	0.15	2.7
	Guadalajara	Perez-Molina	92	1998	Hospital clinical at birth	1993–1995	1 NCIH Hospital	14	19	4	37	1.04	1.41	0.30	2.74
	Guadalajara	Alfaro-Alfaro	93	2002	Hospital Diagnosis at birth	1989–1997	1 hospital				166				1.16
	Guadalajara	Alfaro	94	2004	Hospital Diagnosis at birth	1993–1995	NHCH Hospital	14	19	4	37	1.04	1.41	0.30	2.74
	Mexico City	Valdés	95	1997	Hospital registry	1989–1997	Hospital civil	12	43		55	0.21	0.74		0.95
	Monterrey	Aredondo	96	1990	Hospital medical records	1980–1999	4 Hospital metro Zone	170	183		353	0.95	1.03		1.98
	Monterrey	Hernandez	97	2001	Hospital medical records	1987–1996	Hospital General	12	43		55	0.2	0.74		0.95
	Veracruz	Rodriguez	98	1998	Hospital registry	1987–1988	Hospital Universitario				47			1.76	4.86
	Zacatecas	Macías	99	2000	Hospital registry	1995–1999	Hospital 23	78	52		130	0.59	0.39	0.00	0.98
	National	Mancebo-Hernández	27	2008	Hospital discharge Data	1996–1997	5 Hospitals	7	8	1	16	0.67	0.99	0.12	1.98
						1980–1999	National Information				199				3.7
					1999–2004	1999								0.8	
						2000								0.67	
						2001								0.33	
						2002								0.36	
						2003								0.37	
						2004								0.47	
Peru	Lima	Tarqui-Mamani	100	2009	Hospital medical records	2001–2007	Instituto Nacional Materno Infantil de Lima	48	78	2	128	0.51	0.83	0.02	1.36

Location	Site	Author	Reference Number	Year Publication	Design	Year(s) Reported	Source	Neural Tube Defects Cases			Total live births	Anencephaly	Spina bifida	Encephalocele	NTD Prevalence (An,SB,En) per 1,000 LB									
								Anencephaly	Spina bifida	Encephalocele														
Puerto Rico	National	Dept. of Health	26	2006	Hospital registry	1996–2008	Hospital Regional	2	3	5	2,414	0.82	1.24		2.07									
								50	81	2	133													
								28	65	7	100	63,259	0.44	1.03	0.11	1.58								
								35	52	11	98	64,214	0.54	0.79	0.17	1.53								
								17	40	6	63	60,518	0.28	0.66	0.10	1.04								
								24	32	2	58	59,684	0.4	0.54	0.03	0.97								
								10	30	5	45	59,460	0.17	0.51	0.08	0.76								
								22	26	3	51	55,983	0.39	0.48	0.05	0.91								
								14	25	2	41	52,871	0.26	0.47	0.04	0.77								
								11	15	4	30	50,803	0.22	0.29	0.08	0.59								
S. America		ICBDMS	101, 102	2008	Hospital registry	1974–2006	ECLAMC participating Hospitals	18	24	3	45	51,239	0.35	0.47	0.06	0.89								
								20	25	8	53	50,687	0.39	0.49	0.16	1.04								
								18	10	9	37	48,744	0.37	0.2	0.18	0.76								
								24	26	6	56	46,719	0.51	0.56	0.13	1.19								
								19	17	5	41	45,664	0.42	0.37	0.11	0.9								
								460	438,055															
								903	579,156															
								1433	968,001															
								1721	1,012,539															
								1478	731,513															
Uruguay		Castilla	103	1991	Hospital registry	1982–1988	7 Hospitals ECLAMC	65	52	19	136	1.79	0.68	0.25	1.79									
								59	59	3	56	32,852				1.70								
								59	59	3	86	56,293				1.57								
								104	104	3	56	32,852				1.7								
								105	105	2	52	19,618	1.78	0.76	0.10	2.65								
								106	106	30	14,653	0.89	1.16		2.05									
								Venezuela	Barquisimeto	Moreno Fuennmayor	105	1996	Hospital registry	1993–1996	Hospital universitario	35	15	2	52	1.78	0.76	0.10	2.65	
																13	17	30	14,653	0.89	1.16		2.05	
																103	103	7	136	75,949	1.79	0.68	0.25	1.79
																59	59	3	56	32,852				1.70
59	59	3	86	56,293												1.57								
104	104	3	56	32,852												1.7								

¹ January 2003 to June 2005² July 2005 to december 2007

Table 2

Model-based prevalence rate ratio (PRR) estimates (95% Confidence) for yearly prevalence of neural tube defects for Bogota (Colombia), Costa Rica, Cuba, Dominican Republic, Guatemala City (Guatemala), Mexico, and Puerto Rico

Country/City	Years	Prevalence Rate Ratio (95%CI)	PRR 95% CI	Percent Increase (Decrease) %	95% CI
Colombia/Bogota City	2001 – 2007	0.93	0.76, 1.14	(6.5)	-23.6, 14.4*
Costa Rica	1987 – 2007	0.97	0.96, 0.98	(3.3)	-4.2, -2.3**
Cuba***	1985 – 2006	N/A	N/A	N/A	N/A
Dominican Republic	2000 – 2006	0.92	0.86, 0.99	(7.8)	-14.0, -1.1**
Guatemala City (National Hospitals)	2001 – 2008	0.78	0.74, 0.82	(21.8)	-25.1, -18.2***
Mexico (RYVEMCE)	1980 – 2006	0.95	0.93, 0.97	(4.4)	-6.4, -2.4**
Puerto Rico	1996 – 2008	0.96	0.93, 0.99	(3.5)	-6.6, -0.2**

* Not significant

** P<0.001

*** N/A Not Applicable

Table 3

Fortification status in Latin American countries

Location	Fortification Status	Fortification Regulation Date Wheat Flour	Fortification Status Date Achieved	Folic Acid (ppm)	Fortification Regulation Updated	Folic Acid (ppm)
Argentina ^{35,36}	Mandatory	2002	2002	2.2		
Bolivia ^{35,36}	Mandatory	1996	1998	1.38		
Brazil ^{34,35}	Mandatory	2002	2004	1.5		
Chile ^{35,36}	Mandatory	1997	2000	2.0 – 2.4		
Colombia ^{35,36}	Mandatory	1996	1998	1.54		
Costa Rica ^{35,36,39}	Mandatory	1997	1997	1.3	2003	1.8
Cuba ³⁶	mandatory	1999	2006	2.5		
Dominican Republic ^{35,36}	Mandatory	1997	1998	1.5	2003	1.8
Ecuador ^{35,36}	Mandatory	1996	1996	0.6		2
El Salvador ^{35,36,39}	Mandatory	1996	1996	0.35 – 0.45	2003	1.8
Guatemala ^{35,36,39}	Mandatory	1993	1998	1.08	2003	1.8
Honduras ^{35,36,39}	Mandatory	1993	NA	1.5	2003	1.8
Mexico ^{35,36}	Mandatory	1996	2000	2		1.8
Nicaragua ^{35,36,39}	Mandatory	1997	1999	0.9 – 1.3	2003	1.8
Panama ^{35,36,39}	Mandatory	1997	1999	1.5	2003	1.8
Paraguay ^{35,36}	Mandatory	1998	2000	2.7 – 3.3		
Peru ^{36,37}	Mandatory	2004	2005	1.2		1.2
Puerto Rico ¹⁴	Mandatory	1998	1998	1.4		
Uruguay ³⁸	Mandatory	2006	NA	2.4		
Venezuela ³⁴	None					

* NA=Not available

Table 4

Comparison of Pre- and Post-Fortification Prevalence Rates Ratios for NTDs from Argentina, Brazil, Chile, Costa Rica, Cuba, Mexico, and Puerto Rico.

Country	Fortification Period (years)	N° of Cases	Rate/1,000 live birth	Percent Change	Prevalence Rate Ratios (95% CI)
Argentina	Pre-Fortification (2000)	579	3.20	-45.0%	Referent
	Post-Fortification (2005)	317	1.76		0.55 (0.48, 0.63)
Brazil	Pre-Fortification (2003–2005) ¹	323	3.14	-33.0%	Referent
	Post-Fortification (2005–2007) ²	226	2.43		0.77 (0.64, 0.91)
Chile	Pre-Fortification (1982–1999)	266	1.9	-57.0%	Referent
	Post-Fortification (2001–2003)	28	0.81		0.43 (0.29–0.63)
Costa Rica	Pre-Fortification (1995–1998)	264	1.01	-41.5%	Referent
	Post-Fortification (1999–2004)	236	0.58		0.58 (0.49–0.69)
Cuba	Pre-Fortification (1995–1999)	60	0.26	NA*	Referent
	Post-Fortification (2001–2006)	407	0.88		NA
Mexico (RYVEMCE)	Pre-Fortification (1995–1999)	637	3.58	-59.0%	Referent
	Post-Fortification (2000–2006)	302	1.47		0.41 (0.36–0.47)
Puerto Rico	Pre-Fortification (1996–1997)	198	1.55	-42.5%	Referent
	Post-Fortification (1998–2008)	520	0.89		0.57 (0.48–0.67)

¹ January 2003 to June 2005

² July 2005 to December 2007

* NA = Not applicable. Pre-post-fortification comparison is not possible because Cuban surveillance system changed their inclusion criteria. Post-fortification period included pregnancy terminations and additional hospitals