Global Birth Prevalence of Spina Bifida by Folic Acid Fortification Status: A Systematic Review and Meta-Analysis

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Background. Birth defects remain a significant source of worldwide morbidity and mortality. Strong scientific evidence shows that folic acid fortification of a region's food supply leads to a decrease in spina bifida (a birth defect of the spine). Still, many countries around the world have yet to approve mandatory fortification through government legislation.

Objectives. We sought to perform a systematic review and meta-analysis of period prevalence of spina bifida by folic acid fortification status, geographic region, and study population.

Search methods. An expert research librarian used terms related to neural tube defects and epidemiology from primary research from 1985 to 2010 to search in EMBASE and MEDLINE. We searched the reference lists of included articles and key review articles identified by experts.

Selection criteria. Inclusion criteria included studies in English or French reporting on prevalence published between January 1985 and December 2010 that (1) were primary research, (2) were population-based, and (3) reported a point or period prevalence estimate of spina bifida (i.e., prevalence estimate with confidence intervals or case numerator and population denominator). Two independent reviewers screened titles and abstracts for eligible articles, then 2 authors screened full texts in duplicate for final inclusion. Disagreements were resolved through consensus or a third party.

Data collection and analysis. We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses, or PRISMA, abstracting data related to case ascertainment, study population, folic acid fortification status, geographic region, and prevalence estimate independently and in duplicate. We extracted overall data and any subgroups reported by age, gender, time period, or type of spina bifida. We classified each period prevalence estimate as "mandatory" or "voluntary" folic acid fortification according to each country's folic acid fortification status at the time data were collected (as determined by a well-recognized fortification monitoring body, Food Fortification Initiative). We determined study quality on the basis of sample representativeness, standardization of data collection and birth defect assessment, and statistical analyses. We analyzed study-level period prevalence estimates by using a random effects model (α level of < 0.05) for all meta-analyses. We stratified pooled period prevalence estimates by birth population, fortification status, and continent.

Results. Of 4078 studies identified, we included 179 studies in the systematic review and 123 in a meta-analysis. In studies of live births (LBs) alone, period prevalences of spina bifida were (1) lower in geographical regions with mandatory (33.86 per 100 000 LBs) versus voluntary (48.35 per 100 000 LBs) folic acid fortification, and (2) lower in studies of LBs, stillbirths, and terminations of pregnancy in regions with mandatory (35.22 per 100 000 LBs) versus voluntary (52.29 per 100 000 LBs) fortification. In LBs, stillbirths, and terminations of pregnancy studies, the lowest pooled prevalence estimate was in North America (38.70 per 100 000). Case ascertainment, surveillance methods, and reporting varied across these population-based studies.

Conclusions. Mandatory legislation enforcing folic acid fortification of the food supply lags behind the evidence, particularly in Asian and European countries. This extensive literature review shows that spina bifida is significantly more common in world regions without government legislation regulating full-coverage folic acid fortification of the food supply (i.e., Asia, Europe) and that mandatory folic acid fortification resulted in a lower prevalence of spina bifida regardless of the type of birth cohort. African data were scarce, but needed, as many African nations are beginning to adopt folic acid legislation. (The full article is available online. *Am J Public Health.* 2016;106: 159, e24–e34. doi:10.2105/AJPH.2015.302902)

PLAIN-LANGUAGE SUMMARY

We sought to review the international prevalence of spina bifida. We conducted a systematic review in duplicate by using terms related to spina bifida and epidemiology. We performed meta-analysis stratified by fortification status, birth population, and geographic region. Overall, we identified 4078 articles, with 179 studies included in the systematic review and 123 studies included in a meta-analysis. In studies of live births (LBs), period prevalence estimates of spina bifida from 1985 to 2010 were lower in regions with mandatory (33.86 per 100 000 LBs) versus voluntary (48.35 per 100 000 LBs) folic acid fortification. Period prevalence estimates of spina bifida were also lower in studies of LBs, stillbirths, and terminations of pregnancy with mandatory (35.22 per 100 000 LBs) compared with voluntary (52.29 per 100 000 LBs) fortification. In LBs, stillbirths, and terminations of pregnancy studies, the lowest pooled prevalence estimate was in North America (38.70 per 100 000 LBs). Disparities in spina bifida prevalence remain between countries with and without mandatory folic acid fortification. Even in countries with mandatory folic acid fortification, studies restricted to LBs may underestimate the prevalence of spina bifida and prevalence estimates from LBs only should be interpreted with caution.

Birth defects are one of the leading causes of infant mortality worldwide[1–3] and affect an estimated 1% to 3% of all births.[4] The etiology of many birth defects remains unknown despite a high prevalence and this reality hinders primary prevention efforts. A notable exception to this is the widespread decline in the prevalence of neural tube defects (anencephaly, spina bifida, encephalocele) following the mandatory fortification of grain products with folic acid in several countries.[5–7] Guidelines from the 1990s suggest a daily intake of 400 micrograms for women of reproductive age.[8] Public health messaging aimed at increasing folate consumption has not had the same effect as mandatory folic acid fortification on increasing serum folate levels and reducing the birth prevalence of neural tube defects.[9]

The term spina bifida encompasses a group of birth defects (meningocele, meningomyelocele, myelocele, myelomeningocele, and rachischisis) that are the result of an incomplete closure of the spinal column leading to a herniation or exposure of the spinal cord or meninges.[10] Although spina bifida has a lower case fatality rate than other neural tube defects (approximately 7%, compared with 46% for encephalocele, and 100% for anencephaly),[11] it can result in severe life-long morbidity.[12,13] This likely contributes to the high pregnancy termination rates following prenatal detection of spina bifida.[9,14]

The predictive value of prenatal screening to detect spina bifida and other neural tube defects varies over time and across jurisdictions.[15] An Australian study conducted in the late 1980s concluded that ultrasound was able to detect 75% of pregnancies with spina bifida, and serum screening for α-fetoprotein was able to detect 63% of affected pregnancies, resulting in a combined detection rate of 76% (95% confidence interval [CI] = 69%, 84%).[15] More recent European data suggest that 88% (95% CI = 86%, 90)% of neural tube defects are prenatally diagnosed.[14] Prenatal detection of open lesions (approximately 75% of spina bifida cases) typically has higher detection rates than closed lesions.[15]

Many countries have yet to mandate folic acid fortification of their grain products[16] despite decades-old evidence that dietary supplementation of folic acid significantly decreases cases of neural tube defects, and spina bifida, in particular.[17] Significant gains have been made in reducing child mortality rates, yet neonatal mortality reductions remain elusive because of a paucity of data and wide variations in neonatal health surveillance methods.[18–21] This systematic review provides an overview of international prevalence estimates for spina bifida, a condition still associated with significant childhood morbidity.

The objective of this study was to determine the global prevalence of spina bifida in live births (LBs), stillbirths, and terminations of pregnancy (TOPs) accounting for differential folic acid fortification policies, and to describe regional differences in prevalence.

METHODS

We performed this systematic review and meta-analyses with a well-known protocol (Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA]).[22] The study team generated the search strategy (Appendix A, available as a supplement to the online version of this article at http://www.ajph.org) with input from a research librarian with medical systematic review experience. We searched MEDLINE and EMBASE for articles written in English or French (1985–2010) on December 10, 2010, using terms related to neural tube defects (anencephaly or encephalocele or lipomeningocele or meningocele or myelomeningocele or neural tube defect or spina bifida) and epidemiology (incidence or prevalence or epidemiology). We also hand-searched the reference lists of review articles on the epidemiology of spina bifida and the references of included articles. We included studies reporting on data from 1985 onward because of the advances in neuroimaging and diagnosis since then.

Two study authors independently screened the abstracts and titles of all references in duplicate to find studies on the prevalence of spina bifida (excluding spina bifida occulta). We excluded data if they were not population-based. Two authors then reviewed the selected studies' full text independently and in duplicate. Studies were eligible for the review if they met these criteria: (1) original research, (2) population-based (all cases in a defined geographic area or ascertainment from multiple hospitals or the only hospital in a defined area), and (3) reported an incidence or prevalence estimate or cases of spina bifida per population denominator. If there was disagreement about whether to include a study, the 2 authors would reach consensus through discussion or involve a third author if unable to reach consensus.

Data Extraction and Quality

Two authors abstracted data in duplicate by using a standard data collection form and arrived at agreement. When more than 1 study provided data from the same group of people or jurisdiction (e.g., registry), we included only mutually exclusive data. We included all data if multiple studies reported data from the same group of people but on different time periods or subgroups. We extracted demographic data, diagnostic data including data source(s) and diagnostic criteria, prevalence estimates (i.e., overall and any subgroups reported by age, gender, time period, or spina bifida type), and each country's folic acid fortification status at the time the study was conducted (as determined by a well-recognized fortification monitoring body).[16] We reviewed timing when fortification became mandatory for each individual country and coded individual studies as being in or out of this time frame. For example, mandatory fortification began in the United States in 1998; therefore, studies with

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data collection after that time were in the mandatory fortification period, and studies with data collection before that time were coded as having absent (before 1996) or voluntary fortification (e.g., 1996–1997). We classified any "incidence" estimates in the articles as prevalence estimates, as prevalence is a more appropriate measure to use in birth defect epidemiology. Birth defects are associated with high rates of pregnancy loss; therefore, their detection later in pregnancy or at birth reflects a period of survival.[4,23]

Two authors independently assessed each included study for quality by using a quality assessment tool (Appendix B, available as a supplement to the online version of this article at http://www.ajph.org). The tool was modeled after previous research on quality ratings and established guidelines.[24,25] We assigned a quality score out of 6 based on sample representativeness, standardization of data collection and birth defect assessment, and statistical analyses. Alternatively, we assigned a quality score out of 8 for studies that reported on data from nonregistry or nonadministrative data sources (i.e., those with a possible response rate). We used descriptive statistics to describe study quality scores.

Data Synthesis and Analysis

We analyzed study-level period prevalence estimates by using a random effects model for all meta-analyses. We detected between-study heterogeneity by using the Cochran Q statistic and we used I^2 to quantify the magnitude of between-study heterogeneity. We stratified pooled period prevalence estimates by birth population, fortification status, and continent. If a prevalence estimate spanned pre- and postfortification time periods, we did not pool it for the meta-analysis. We investigated publication bias visually with funnel plots and statistically using the Begg and Egger test.

For all tests, we used an α level of less than 0.05 for significance. We performed all analyses in R version 2.14 (R Foundation for Statistical Computing, Vienna, Austria). We used the META package to produce the pooled estimates, forest plots, and publication bias assessment.

RESULTS

The search strategy yielded a total of 3336 citations: 1446 from MEDLINE and 1890 from EMBASE (Figure 1). After the initial screen, 738 articles met the criteria for full-text review, of which we excluded 600. Hand searching resulted in the inclusion of 41 additional articles. Characteristics of all 179 studies included in the systematic review are shown in Appendix C (available as a supplement to the online version of this article at http://www.ajph.org). From the 179 eligible studies overall, 123 studies included sufficient information to calculate period prevalence estimates between 1985 and 2010 and we thus included these in the meta-analyses.

Of the 179 included studies, all reported on the epidemiology of spina bifida.[5–7,10,17,2–199] Of the studies, 92 reported on data from North America, 46 from Europe, 31 from Asia, 7 from Australia, 4 from South America, and 3 from Africa. (Some studies report on data from more than 1 continent.)

Prevalence of Spina Bifida

All included studies (Appendix C, available as a supplement to the online version of this article at http://www.ajph.org), reported the period prevalence of spina bifida, and we included data from 123 studies (indicated by an asterisk in Appendix C) in the meta-analysis. We could not include studies that did not provide 1 of the following combinations in the meta-analysis portion of the systematic review: (1) numerator cases plus sample denominator, (2) prevalence estimate with confidence intervals, or (3) cases or sample with prevalence estimate.

Studies in the meta-analysis also had to consist of an LBs-only sample, or LBs plus stillbirths, or LBs plus stillbirths plus TOPs. We did not generate a single global pooled prevalence as there was a great deal of heterogeneity based on fortification status, study population (e.g., LBs-only vs LBs plus stillbirths plus TOPs), and geographic variation (Table 1).

Sources of Heterogeneity

Study population. Estimates of the pooled period prevalence of spina bifida varied depending on the population studied (Tables 1 and 2). Studies including only LBs (Appendix D, available as a supplement to the online version of this article at http://www.ajph.org) reported a pooled period prevalence of 38.93 per 100 000 (95% CI = 35.77, 42.36). In studies reporting on LBs and stillbirths (Appendix E, available as a supplement to the online version of this article at http://www.ajph.org), the pooled period prevalence was 43.59 per 100 000 (95% CI = 40.07, 47.41). Finally, studies reporting on LBs, stillbirths, and TOPs (Appendix F, available as a supplement to the online version of this article at http://www.ajph.org) reported a pooled prevalence of 47.63 per 100 000 (95% CI = 43.05, 52.70).

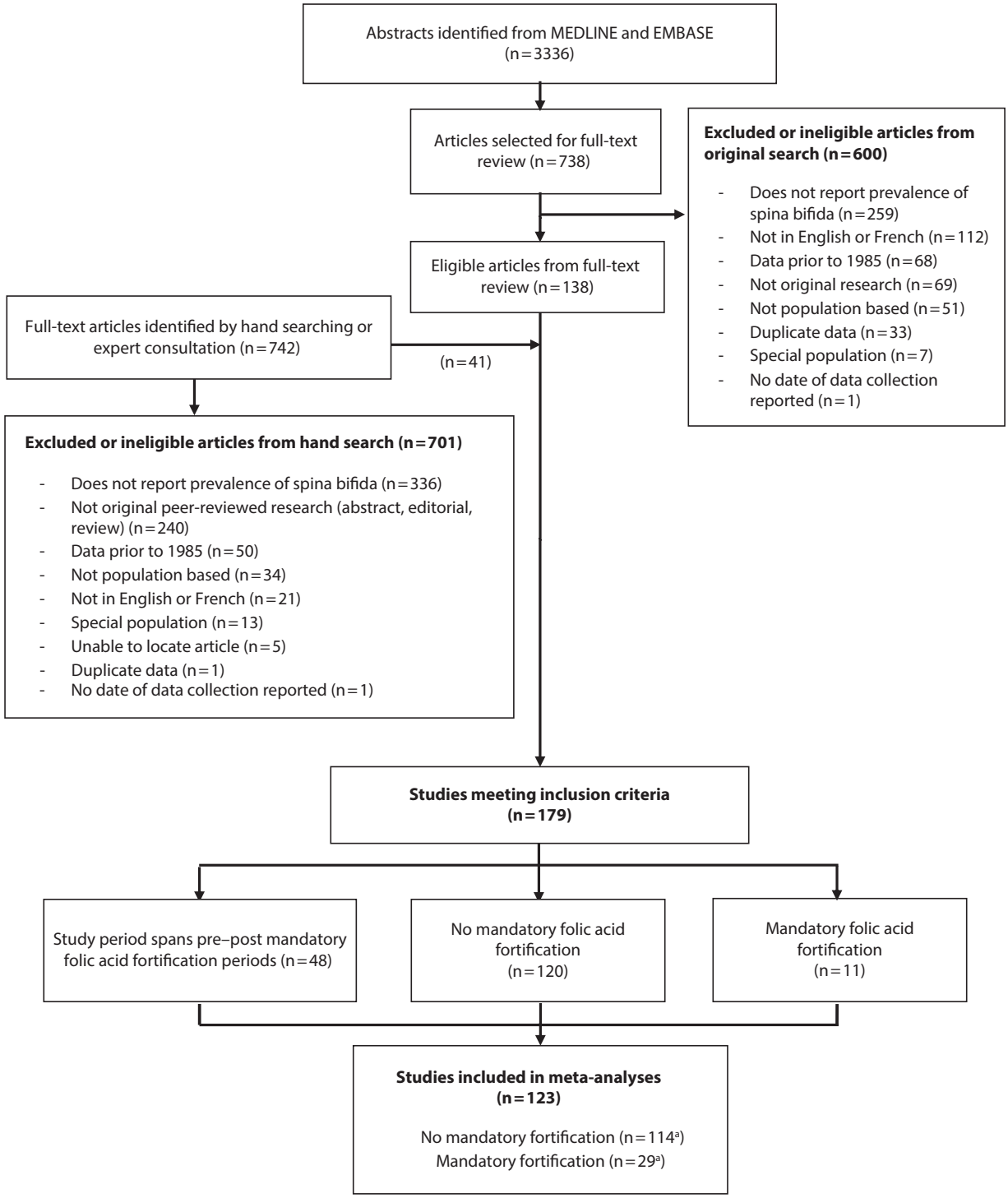
Fortification level. In those studies reporting only on LBs, the pooled prevalence of spina bifida was lower in studies in which folic acid fortification was mandatory (33.86 per 100 000; 95% CI = 31.05, 36.92) as opposed to studies in which fortification was voluntary or nonexistent (48.35 per 100 000; 95% CI = 41.07, 56.93).

For studies reporting on LBs and stillbirths, the pooled prevalence of spina bifida in studies in which folic acid fortification was mandatory (30.37 per 100 000; 95% CI = 27.42, 33.63) was lower than the pooled prevalence in those studies in which fortification did not exist or was voluntary (47.74 per 100 000; 95% CI = 43.66, 52.20).

The pooled prevalence of spina bifida in studies reporting on LBs, stillbirths, and TOPs in which there was mandatory folic acid fortification (35.22 per 100 000; 95% CI = 32.18, 38.56) was lower than in studies in which there was voluntary or no fortification (52.29 per 100 000; 95% CI = 46.28, 59.08).

Continent. In studies reporting on LBs only (Appendix G, available as a supplement to the online version of this article at http://www.ajph.org), there was no statistically significant difference between any continents in the pooled prevalence of spina bifida: Africa (78.81 per 100 000; 95% CI = 30.66, 202.55), Asia (81.37 per 100 000; 95% CI = 35.05, 188.90), Australia (37.69 per 100 000; 95% CI = 10.51, 135.21), Europe (59.76 per 100 000; 95% CI = 39.19, 91.12), and North America (36.87 per 100 000; 95% CI = 34.36, 39.55). However, limited data were available from Africa (3 studies, 176 births), Asia (22 studies, 3378 births), and Australia (5 studies, 1047 births) resulting in wide confidence intervals.

There was even greater variability among continents in the pooled prevalence of spina



[a]Some studies contributed more than 1 estimate.

FIGURE 1—Spina Bifida Prevalence Systematic Review Flow Diagram

TABLE 1—Pooled Period Prevalence of Spina Bifida per 100 000 Births by Birth Population and Fortification Status (Meta-Analysis): World Population, 1985–2010

	Fortification Mandatory		Fortification Not Mandatory	
Birth Population	No. of Studies	Prevalence (95% CI)	No. of Studies	Prevalence (95% CI)
Live births	14	33.86 (31.05, 36.92)	34	48.35 (41.07, 56.93)
Live births and stillbirths	13	30.37 (27.42, 33.63)	37	47.74 (43.66, 52.20)
Live births, stillbirths, and terminations of pregnancy	14	35.22 (32.18, 38.56)	49	52.29 (46.28, 59.08)

Note. CI = confidence interval.

bifida in studies reporting on both LBs and stillbirths (Appendix H, available as a supplement to the online version of this article at http://www.ajph.org). The pooled prevalence was lowest in North America (36.08 per 100 000; 95% CI = 33.50, 38.87) and highest in Asia (87.99 per 100 000; 95% CI = 66.83, 115.86) and this was a significant difference. Estimates from South America (81.33 per 100 000; 95% CI = 59.56, 111.06) were also significantly higher than those from North America. One study from Africa reported a prevalence of 54.32 per 100 000 (95% CI = 36.71, 80.39), which was not significantly different from estimates from the other continents. Australian studies had a pooled prevalence of 51.48 per 100 000 (95% CI = 42.98, 61.66) and European studies had a pooled prevalence of 59.54 per 100 000 (95% CI = 32.98, 107.49), which were not significantly different from other continents.

North America also had the lowest pooled prevalence of spina bifida in studies reporting on LBs, stillbirths, and TOPs (Appendix I, available as a supplement to the online version of this article at http://www.ajph.org; 38.70 per 100 000; 95% CI = 34.41, 43.53). This was significantly lower than estimates from all other continents, among which there were no differences. The estimate from Asia was 243.14 per 100 000 (95% CI = 48.34, 1223.04); Australia, 61.66 per 100 000 (95% CI = 51.44, 73.91); and Europe, 52.73 per 100 000 (95% CI = 45.43, 61.21).

Publication Bias and Study Quality

For the period prevalence of spina bifida, we did not find significant funnel plot asymmetry for the Begg or Egger test ($P > .05$). Upon visual inspection, the funnel plot appeared symmetrical.

The median study quality score for studies reporting on the incidence or prevalence of spina bifida was 3 out of 6 (range = 1–5). One hundred seventy-seven studies described the target population in detail and 176 sampled either the entire population or used probability sampling (Appendix J, available as a supplement to the online version of this article at http://www.ajph.org). The majority of studies used registries or administrative data, and as such a response rate was not ascertained. In those studies that necessitated a response rate, 2 of the 3 studies did report a response rate, though none stated whether it was greater than 70%. Most studies reported a sample that was representative of the target population (138/179). It was unclear in 100 studies whether standardized data collection methods were used and only 20 reported using validated criteria to assess for the presence of spina bifida. Finally, the majority of the studies (147/179) did not report estimates with their accompanying CIs or by subgroups.

DISCUSSION

This study presents a comprehensive systematic review of the literature on the global prevalence of spina bifida. We performed meta-analyses to obtain estimates of spina bifida prevalence in subgroups of LBs, stillbirths, and TOPs in countries with or without mandatory folic acid fortification. Canada and the United States were the first countries to require mandatory fortification and multiple studies have documented a pre–post reduction in neural tube defects.[64] Currently, most studies in North America, South

TABLE 2—Summary of Meta-Analysis Results Regarding Spina Bifida per 100 000 Births by Birth Population and Fortification Status: World Population, 1985–2010

Variable and Group	No. of Studies	Estimate per 100 000 Births (95% CI)
Fortification: mandatory		
LB	14	33.86 (31.05, 36.92)
LB + SB	13	30.37 (27.42, 33.63)
LB + SB + TOP	14	35.22 (32.18, 38.56)
Fortification: not mandatory		
LB	34	48.35 (41.07, 56.93)
LB + SB	37	47.74 (43.66, 52.20)
LB + SB + TOP	49	52.29 (46.28, 59.08)
Continent: Africa		
LB	2	78.18 (30.66, 202.55)
LB + SB	1	54.32 (36.71, 80.39)
LB + SB + TOP	. . .	. . .
Continent: Asia		
LB	6	81.37 (35.05, 188.90)
LB + SB	14	87.99 (66.83, 115.86)
LB + SB + TOP	4	243.14 (48.34, 1223.04)
Continent: Australia		
LB	1	37.69 (10.51, 135.21)
LB + SB	1	51.48 (42.98, 61.66)
LB + SB + TOP	4	61.66 (51.44, 73.91)
Continent: Europe		
LB	5	59.76 (39.19, 91.12)
LB + SB	2	59.54 (32.98, 107.49)
LB + SB + TOP	22	52.73 (45.43, 61.21)
Continent: North America		
LB	29	36.87 (34.36, 39.55)
LB + SB	23	36.08 (33.50, 38.87)
LB + SB + TOP	29	38.70 (34.41, 43.53)
Continent: South America		
LB	. . .	. . .
LB + SB	3	81.33 (59.56, 111.06)
LB + SB + TOP	. . .	. . .

Notes. CI = confidence interval; LB = live birth; SB = stillbirth; TOP = termination of pregnancy. The pooled period prevalence of spina bifida in studies reporting on live births, stillbirths, and terminations of pregnancy was lower in regions with mandatory folic acid fortification than in those without (35.22 per 100 000 live births compared with 52.29 per 100 000 live births, respectively).

America, and Oceania have mandatory fortification; many African countries (e.g., Burkina Faso, Morocco)[16] are implementing mandatory fortification. Fortification is uncommon in Asia and Europe. A higher prevalence of spina bifida was seen in countries without mandatory folic acid fortification policies in place at the time of data collection for the studies included in this systematic review. We found significant geographic variation in terms of spina bifida prevalence in studies including LBs, stillbirths, and TOPs; North American prevalence estimates were lower than all other continents. When LBs and stillbirths were reported together, North America had the lowest prevalence of spina bifida and Asia had the highest.

These regional differences reflect different regional policies with regard to folic acid fortification. It is also important to note the large number of prevalence estimates provided by ethnic subgroups in some American studies.[127,128] One study[200] reported a period prevalence for Arizona in 1997 of 4.23 per 10 000 births in a non-Hispanic White sample whereas the corresponding prevalence estimate for the non-Hispanic Black or African samples was 0. Many African countries have recently instituted mandatory fortification and the impact of this in changing global rates of spina bifida will need to be assessed. Furthermore, access to prenatal screening, pregnancy termination, and differing folic acid fortification policies will also produce local and widespread variations in international comparisons such as this.

Policymakers are often challenged to make decisions with imperfect evidence of benefit or harm that have an impact on the health of the population.[201] Mandatory folic acid fortification for the prevention of neural tube defects is one such issue in which a global disparity exists. As of July 2012, 67 counties had fortified their wheat flour with folic acid (mandatory or voluntary programs), affecting approximately 2.2 billion people.[16] As the neural tube closes early in gestation (day 28), public health campaigns aimed at encouraging pregnant women to use multivitamins containing folic acid often come too late, as many women do not realize that they are pregnant at this stage.[9] An economic evaluation conducted in the United States almost 10 years after mandatory folic acid fortification estimated that the cost savings from this initiative ranged from $88 million to $142 million annually.[202] A systematic review of cost of illness studies similarly concluded that folic acid fortification was cost-effective in all studies.[12] This detailed review highlights the strong evidence in favor of mandatory and full coverage of grain fortification for prevention of spina bifida.[9,201]

We identified several important sources of heterogeneity when extracting data for this systematic review. The first relates to the classification of infants with multiple malformations. Some sources only count the most serious birth defect whereas others count all defects. One review showed that including joint cases of anencephaly and spina bifida in prevalence estimates of spina bifida creates an inflation of the prevalence of spina bifida[203]; however, consistent international definitions of what explicitly should and should not be included in counts of spina bifida have not been established (e.g., studies that reported on spina bifida without anencephaly may underestimate the true prevalence).

The second source of heterogeneity involves the variability of methods of case ascertainment for spina bifida (e.g., birth defects surveillance systems, prospective clinical evaluation of all infants, retrospective chart review). The validity of each source of data has not been established and it is unknown what proportion of spina bifida cases are truly captured by each source. Different forms of ascertainment (e.g., birth certificates, surveillance systems) ascertain spina bifida in different ways with varying degrees of validity[204]; however, studies conducted to date suggest that almost all data sources suffer from some degree of underreporting[203,205] and US data suggest that prevalence estimates for spina bifida are robust across various sources of ascertainment, particularly those characterized by local and national collaboration.[206] Reaching neonatal mortality targets set forth by Millennium Development Goal 4 (to reduce under-5 mortality by two thirds) requires local and national networks aimed at scaling up both active newborn health surveillance systems and newborn health programs.[207]

A third source of heterogeneity relates to the studies' inclusion criteria (i.e., LBs-only compared with LBs, stillbirths, and TOPs). Differences remain in which populations are included in reported data, in that a sizable number of studies did not include data on TOPs. Although it is recognized that these data may be more difficult to obtain, this challenge should not negate the importance of this information in international comparisons. Differences in birth prevalence estimates may reflect differing genetic susceptibility, differential patterns of folic acid consumption, or different policies on TOP.[203] In addition, because ultrasonography and prenatal biochemical screening are standard parts of prenatal care in many parts of the world, spina bifida is often detected prenatally. Because of differential patterns of pregnancy termination for fetuses with birth defects compared with nonmalformed fetuses, failure to account for pregnancy terminations likely introduces selection bias into prevalence estimates, underestimating observed associations.[208]

Spina bifida prevalence remains high in some regions despite policies promoting prenatal folic acid supplementation and fortification of the food supply. Health promotion strategies that encourage women of reproductive age to take folic acid supplements have failed.[209] A recent study showed that the proportion of women taking their supplements in England decreased from 35% in 1999 to 2001 to 31% in 2011 to 2012.[209] Fortification efforts should also address differences in the amount of folic acid that women receive from a fortified food supply. A recent review[210] showed that the target population of women of reproductive age who live in countries with mandatory folic acid fortification do not necessarily receive the daily recommended dose of 400 micrograms folic acid. In fact, the daily folic acid amount that is ingested in countries with national coverage programs can vary from 32.8 micrograms (Niger) to 736.7 micrograms (South Africa). Infrastructure that comprehensively addresses neonatal health surveillance, as well as micronutrient fortification, is vital for accelerating the reduction in neonatal mortality that we have observed, particularly in Asian and African regions.[21,211]

This study is not without limitations. We did not include terms related to congenital anomalies and birth defects in the original search strategy as this study was specifically focused on spina bifida. This may have

resulted in some studies being missed. However, because of the number of studies that we included and the fact that we hand-searched all of the reference lists of included articles, if any studies were not included, we do not anticipate them altering the pooled prevalence estimates. A second limitation concerns the differences between studies in defining the study population. There is no gold-standard diagnostic method for spina bifida and as such we may expect there to be a degree of underreporting in low- and middle-income regions where access to genetic testing and imaging could be lower. However, we found higher rates of spina bifida in low- and middle-income regions and we expect the risk of measurement bias to be negligible.

This systematic review provides global prevalence estimates of spina bifida across different regions, birth populations, and folic acid fortification policies. Spina bifida remains a significant source of worldwide infant mortality and morbidity despite decades-old evidence of the protective effects of dietary folic acid supplementation. Gross disparities exist across and between continents in terms of micronutrient food fortification legislation, food supply coverage, and per capita folic acid intake. Folic acid supplementation for spina bifida is not yet being used to its full potential and the worldwide implementation of mandatory folic acid fortification legislation is long overdue. AJPH

CONTRIBUTORS

All authors made a substantial contribution to this work. All authors approved the final article for intellectual content with approval for publication with agreement toward accountability for all aspects of the article in regards to accuracy and integrity. C. A. M. Atta was involved in data collection, data analysis, data interpretation, drafting of the article, and critical revision of the article. K. M. Fiest contributed to the literature search, data collection, data analysis, data interpretation, drafting of the article, creation of the figures, and critical revision of the article. A. D. Frolkis contributed to data collection, data analysis, data interpretation, and critical revision of the article. N. Jette was involved in obtaining operating funds for the study, literature search, study design, data collection, data analysis, data interpretation, and article writing. She also approved the final article and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. T. Pringsheim was involved in obtaining operating funds for the study, literature search, study design, data collection, data analysis, and data interpretation. She was involved in revising the work critically for important intellectual content and gave final approval of the version to be published. C. St Germaine-Smith made contributions to the literature search, study design, and data collection, and critically reviewed the article. T. Rajapakse was involved in acquisition and analysis of data and reviewed the final article for intellectual content with approval of the final article for publication with agreement toward accountability for all aspects of the article in regards to accuracy and integrity. G. G. Kaplan was involved with interpretation of data and critical revision of the article. A. Metcalfe contributed to the data collection, data analysis, data interpretation, drafting of the article, and critical revision of the article.

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HUMAN PARTICIPANT PROTECTION

Study protocol approval was not needed for this study because it only used publicly available aggregate data.

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