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REVIEW

Historical perspective on folic acid and challenges in estimating global prevalence of neural tube defects

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Neural tube defects (NTD) are major congenital malformations affecting births worldwide. NTD are associated with life-long disability, significant medical care costs, and child mortality. Their prevalence varies worldwide. We conducted a review of published literature and surveillance systems to examine challenges in estimating an overall global prevalence estimate for NTD. Our review showed that most low- and middle-income countries do not track NTD and indicate a high prevalence of these malformations where data are available. Challenges in global NTD prevalence estimation include (1) quality of surveillance methods, (2) existing risk factors (including geographic or socioeconomic factors, availability and use of folic acid, and racial–ethnic and genetic factors), and (3) limitations in education and access to care. We recommend population-based surveillance systems tracking all pregnancy outcomes and major risk factors. Countries should invest in sustainable, multisource surveillance systems, in parallel to folic acid interventions, for gaining a more accurate knowledge of global prevalence of NTD than we currently have. Such efforts will assist in both global prevention of NTD and periodic evaluation of folic acid interventions for NTD reduction. Global NTD prevalence data can drive political will and accelerate the implementation and evaluation of NTD prevention programs.

Keywords: anencephaly; neural tube defects; prevalence; spina bifida; surveillance

Introduction

Neural tube defects (NTD) are one of the most common types of congenital malformations characterized by incomplete closure of the embryonic neural tube.¹ Anencephaly and spina bifida are the two most common types of NTD that affect the brain and spinal cord, respectively.²–⁴ These defects occur between 21 and 28 days after conception when most women are unaware of their pregnancies.¹ NTD contribute to stillbirths, as well as neonatal, infant, and under-five mortality; along with life-long disability and substantial health care costs among those who survive.⁵

The March of Dimes Global Report on Birth Defects, using methods developed by Modell and colleagues, published a global estimate of number of live births with NTD.⁵ According to this report, an estimated 324,000 births (2.4 per 1000 live births) were affected by NTD globally during the year 2001, which contributed to over 2.3 million disability-adjusted life years.⁵ Recently, Blencowe et al. extended the Modell methodology and estimated 260,100 NTD-affected pregnancies worldwide in 2015, of which approximately 50% were electively terminated.⁶ Over 75% of NTD-affected births resulted in death by 5 years of age.⁶ The global prevalence of NTD was estimated by Blencowe and colleagues to be 1.86 per 1000 live births in 2015, while varying in different regions of the world between 0.75 and 3.12 per 1000 live births.⁶

A comprehensive systematic review of peer-reviewed literature, birth defects surveillance registries, and reports published between January 1990 and July 2014 on the prevalence of NTD worldwide by Zaganjor and colleagues listed many limitations.

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in surveillance of birth defects in low- and middle-income countries (LMIC), and that the higher the income status of a country, the higher the likelihood of having NTD surveillance.\(^7\)

A historical account of maternal folate insufficiency and its role in the occurrence of NTD in the offspring is an important consideration in the prevalence of NTD worldwide. Folic acid insufficiency is a well-established risk factor associated with the majority of cases of NTD globally. The estimated prevalence of NTD using robust population-based assessment, before the availability of elective termination of pregnancy for fetal anomalies (ETOPFA) and before mass folic acid interventions were implemented to prevent NTD, could serve as a proxy to understand the current prevalence of NTD in countries where surveillance is lacking.

**Historical perspective of folic acid and NTD**

Ecological studies documenting NTD outcomes during the Dutch famine (1944–1946) were some of the first epidemiological studies to show the link between prenatal nutrition and NTD.\(^8\) Between years 1947 and 1956, Renwick reported a high number of anencephalic stillbirths during the year subsequent to a widespread potato blight disease.\(^9\) However, two subsequent studies, one by Smith \textit{et al.} in Edinburgh between years 1954 and 1970\(^10\) and another by MacMahon \textit{et al.} in Boston between 1930 and 1964,\(^11\) showed no association between exposure to potato blight and an increased prevalence of NTD.

During the 1950s and 1960s, biochemical studies established that folates were essential for single carbon unit transfer to convert homocysteine to methionine, DNA methylation, and other cellular reactions.\(^12\) During this period, folate was identified to be integral in rapid tissue growth and cell division in pregnancy and fetal development, and that pregnancy imposed an increased need for dietary folate to accommodate tissue growth and cell differentiation.\(^13,14\) Hibbard observed that marginal folate levels among pregnant women increased their risk for fatal macrocytic anemia and NTD.\(^15\)

A multisource, population-based birth registry study in Belfast, Ireland, conducted between 1964 and 1968, was one of the first studies to examine the prevalence of NTD in both stillbirths and live births.\(^16\) This study reported a prevalence of 4.2 per 1000 live and stillbirths for anencephaly (with or without spina bifida) and 4.5 per 1000 live and stillbirths for spina bifida alone, yielding a combined prevalence of 8.7 per 1000 live and stillbirths.\(^16\) There was a considerable variation in both prevalence and survival of those affected with spina bifida between different electoral wards in Belfast, indicating a higher risk in neighborhoods with lower socioeconomic status and overcrowding. A study conducted in Newfoundland, Canada, between 1976 and 1980 reported a combined prevalence of spina bifida and anencephaly to be 3.1 per 1000 total births.\(^17\) There were significant temporal and geographic variations, with St. John’s census region reaching a prevalence of 8.9 per 1000 live births for spina bifida.\(^17\) At this time, there was still no knowledge of the role of maternal nutrition in NTD etiology.

Elwood and Scott suggested the role of vitamin supplementation in observed declines in the prevalence of anencephaly in Ireland and England.\(^18\) In 1983, the UK’s Medical Research Council initiated a double-blind, randomized trial to study the effects of folic acid on the offspring of women who previously had an NTD-affected birth.\(^19\) This study, published in 1991, provided strong evidence that folic acid prevented up to 70% of the cases in the intervention arm compared with the group that did not receive any intervention.\(^19\)

A World Health Organization (WHO) guideline was published in 2015 for countries to take actions for achieving optimal folate concentrations in women of reproductive age. The recommendation proposes a threshold at a population level, for red blood cell (RBC) folate concentrations to be above 400 ng/mL (906 nmol/L), for achieving greatest reductions in NTD.\(^20\) Crider \textit{et al.} reported an estimated NTD prevalence of 0.6 per 1000 total births (including live births, stillbirths, and ETOPFA) can be achieved through effective folic acid-based prevention strategies.\(^21\) Most countries with mandatory food fortification policies have achieved NTD prevalence estimates near 0.6 per 1000 total births;\(^22–25\) however, in countries without such policies, the average prevalence is about 2.5 per 1000 live births, with some countries as high as 10–20 per 1000 live births.\(^5,26,27\) In countries where fortification has been implemented to a large extent, it has been noted that there can still be a variability in the NTD prevalence as a function of effectiveness of folic acid fortification implementation.
methods, and genetic and dietary characteristics of the population.28

Global prevalence of NTD

Knowledge of global prevalence of NTD, obtained using valid data from all countries, will help us understand the magnitude of the burden of NTD worldwide and to prevent disparities in prevalence and prevention. We reviewed published literature and birth defects surveillance systems to examine an overall global prevalence estimate of NTD and to summarize challenges in such estimation process. We considered that the current period in LMIC, where NTD surveillance and folic acid interventions lack, may mimic the circumstances and quality of life factors of populations living during the 1960s and 1970s in countries where NTD surveillance existed.

Methods

We searched PubMed for studies published between 1960 and 2016 on the prevalence of NTD. Key search terms included: neural tube defects, spina bifida, anencephaly, birth defects, congenital anomalies, and prevalence. We specifically focused on meta-analyses and systematic reviews published since 2010 on global prevalence of NTD. We also examined data from selected birth defects monitoring programs and surveillance networks that report prevalence data from birth defects surveillance (e.g., European surveillance system of congenital anomalies (EUROCAT)).

Global prevalence of NTD, for the purpose of our review, was defined as the total number of cases with NTD worldwide divided by total number of births in the world. We have elected to express this estimate per 1000 births in our review.

Findings from published studies

In the systematic review conducted by Zaganjor et al., there were only 160 unique studies and reports on NTD prevalence worldwide that met the criteria for their review.7 They examined data from studies that included at least 5000 total births in 75 countries between 1990 and 2014. Among them, a majority were from North America, followed by Europe. There was a dearth of studies from Africa, South America, and Asia. Additionally, most studies did not include ETOPFA. Results were stratified by WHO regions and World Bank income classification. Median (range) NTD prevalence (per 1000 total births) varied from 1.2 (0.5–7.5) in Africa, 2.2 (0.2–12.4) in the Eastern Mediterranean, 0.9 (0.1–3.6) in Europe, 1.2 (0.3–2.8) in the Americas, 1.6 (0.2–6.6) in South East Asia, and 0.7 (0.03–19.9) in the Western Pacific. None of the low-income countries had either national or regional surveillance systems for birth defects. About 25% and 70% of lower middle and upper middle income countries, respectively, reported having a malformations registry.7

A systematic review and meta-analysis of studies on spina bifida was published by Atta et al. They examined the country-level prevalence of spina bifida by folic acid fortification status, geographic region, and study population.29 The study eligibility criteria allowed 179 studies in the systematic review and 123 studies for inclusion in meta-analysis as population-based studies that reported prevalence estimates for spina bifida between 1985 and 2010. This review found a large heterogeneity in the mean prevalence of spina bifida depending on the pregnancy outcome included in the denominator. Spina bifida prevalence among live births alone was 0.38 per 1000 (95% confidence interval (CI) = 0.36–0.42), prevalence among live births and still births combined was 0.44 per 1000 (95% CI = 0.40–0.47), and total prevalence (including live births, stillbirths, and ETOPFA) was 0.47 per 1000 (95% CI = 0.43–0.52). Spina bifida prevalence was significantly lower in studies from countries where folic acid fortification was mandatory (0.34 per 1000 live births; 95% CI = 0.31–0.37) compared with studies from countries where fortification was voluntary or nonexistent (0.48 per 1000 live births; 95% CI = 0.41–0.57). The same effect was noted when including other birth outcomes (i.e., stillbirths and ETOPFA), where countries with mandatory fortification had a lower pooled prevalence of spina bifida compared with countries without such an intervention. Limited data were available from Africa, Asia, and Australia compared with Europe and North America.29

Findings from surveillance systems

EUROCAT was established in 1980 and serves as a central data repository for population-based surveillance of birth defects from 28 member registries in 18 countries tracking live births, stillbirths, and ETOPFA.30 These data are mostly representative of high-income countries (HICs). EUROCAT
data indicate that in Europe, about 5000 pregnancies are affected with NTD annually, with a majority of those terminated prenatally. Between 1991 and 2011, the total prevalence of NTD was 0.9 per 1000 live and stillbirths, with anencephaly prevalence at 0.33 and spina bifida prevalence at 0.46. There was no clear upward or downward trend in the overall prevalence during this period; however, there was a substantial decrease in live birth prevalence to a large extent for anencephaly and to a lesser extent for spina bifida, both attributable to prenatal diagnosis and ETOPFA. 30

Between years 1983 and 2003, an analysis of 15 population-based surveillance registries that were members of the International Clearinghouse on Birth Defects Surveillance and Research from Europe, Australia, Canada, and the United States showed the prevalence of NTD varied by surveillance system. These registries surveyed more than 10,000 births per year, ascertained pregnancy terminations due to congenital malformations, and had official public health policy for folic acid use or implemented food fortification. Also, in countries that implemented folic acid fortification (i.e., Australia, United States, and Canada), there was a strong downward trend in the prevalence of NTD in the postfortification period, with prevalence ratios ranging between 0.65 and 0.90 for NTD prevalence before and after fortification. 31

Challenges in estimation of global prevalence of NTD

Our review of literature identified the following key areas in NTD surveillance that posed challenges in estimation of global prevalence and led to a variability of burden.

Surveillance methods

Congenital malformations are not viewed as top causes of child mortality. 5 This is partly due to lack of data on causes of death in countries with the highest child mortality rates. Hence, they are not prioritized for surveillance as compared with other birth outcomes that more visibly contribute to child mortality. 5 In comprehensive reviews of existing studies and surveillance systems, it has been consistently pointed out that several LMIC lack systems for identifying birth defects or mandatory reporting by health care providers. 6,7,29 Among countries with surveillance systems, ascertainment varies depending on the type of surveillance (population based versus hospital based) and its completeness. Abstracting data from multiple sources yields a more robust estimate of prevalence compared with that obtained using a single source. Variability can result from the quality of data source (e.g., hospital discharge data, hospital delivery logs, and vital records). In countries where a large proportion of births occur at home, utilizing hospital-based sources alone would understate prevalence. Clinical definition for NTD, case diagnosis, and confirmation process are not standardized. Data confirmed by trained personnel such as medical geneticists or pediatricians would yield robust prevalence estimates with higher diagnostic specificity. 7

Missing data are a significant concern for global prevalence estimation of NTD. Systematic capability of utilizing multiple data sources enhances completeness of case ascertainment. Many published studies from LMIC lack a clear description of their study methods, data collection procedures, and definitions of what constitute the numerator and denominator in the prevalence equation. 7 Information on availability of prenatal screening and policies on elective terminations following a fetal diagnosis of NTD allows a better interpretation of prevalence and long-term trends. Several countries do not track birth defects in pregnancies that result in stillbirths, early fetal losses, or elective terminations after a diagnosis of NTD. 7

Risk factors

Variability in the prevalence of NTD can result from known risk factors, including geographic or socioeconomic factors, availability and use of folic acid, and racial–ethnic and genetic factors.

Geographic or socioeconomic factors. Geographic variability in the prevalence of NTD is well documented. 5–7 In-country variability also exists and is reported in the United States, 22 Canada, 23 India, 26 and China. 32 Geographic variations in prevalence can be a function of regional differences in populations, both in terms of variable dietary choices and access to foods that provide adequate dietary folates. For example, the northern provinces of China are economically poorer compared with the southern provinces, leading to a significant difference in people’s diet and access to folate-rich foods. 32 Prevalence of NTD is observed to be lower
among HIC as compared with LMIC.\textsuperscript{5,6} Regional variations in prevalence can be a function of socioeconomic status of neighborhoods and dietary customs and practices that interfere with access to and use of foods fortified with folic acid.\textsuperscript{16,33}

**Availability and use of folic acid.** Countries with mandatory policies on folic acid fortification of staple foods have a significantly lower prevalence of NTD compared with countries that have no fortification, or just voluntary fortification or folic acid supplementation programs.\textsuperscript{29} Even within countries with mandatory folic acid fortification policies, the prevalence can vary on the basis of the penetration of the fortification program, with pockets of high prevalence in regions that do not have access to fortified foods. Countries with mandatory fortification that are homogeneous have an even higher likelihood of having better effectiveness than countries that have subgroups of their population with poor access or availability of fortified staples and dietary customs. An example of this is Guatemala that has a national policy on mandatory fortification of wheat and maize, and yet a wide variation in the RBC folate concentrations is reported among women of reproductive age within the country. Indigenous Guatemalan populations living in rural, low-income regions were at a higher risk of NTD compared with women in urban areas of the country as indigenous populations process their own corn and do not consume fortified products.\textsuperscript{33} Aborigines in Australia had a twofold increased risk of NTD compared with non-Aborigines because folic acid supplements failed to reach Aboriginal women of reproductive age.\textsuperscript{2} This disparity was subsequently resolved with the implementation of mandatory fortification of flour in Australia that reached everyone in the country.\textsuperscript{2}

**Racial–ethnic and genetic factors.** The methylenetetrahydrofolate reductase (MTHFR) 677C>T polymorphism is a risk factor for NTD, and the prevalence of MTHFR 677TT genotype varies by ethnicity and regions, from <2\% in some African populations to >35\% in northern Chinese and those of Mexican origin.\textsuperscript{34,35} Mothers or infants with the TT genotype have significantly increased odds of NTD compared with their counterparts with the CC genotype.\textsuperscript{36–38} Hispanic populations in the United States are at a higher risk of NTD, which could be partly explained by their staple food (unfortified corn masa) and because of a higher prevalence of genetic factors associated with NTD.\textsuperscript{22,39}

**Education and access to care**
Preconception education and access to healthcare, including legal services for ETOPFA, predict NTD prevalence in countries. For example, many

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**Figure 1.** Distribution of population-based prevalence (per 10,000 births) of neural tube defects by birth outcome, Ireland 2009–2011. Data from McDonnell et al.\textsuperscript{50}
countries in Europe have universal health care guidelines for periconceptional folic acid use (in the absence of mandatory fortification) and services for ETOPFA. EUROCAT reports that ~80% of pregnancies in Europe are electively terminated after a diagnosis of NTD prenatally, and that only 10–30% of European women report taking the recommended dose of folic acid supplements preconceptionally.40-42 LMIC have limited access to preconception or prenatal counseling and healthcare, and birth defects do not receive attention or priority. There is a clear lack of surveillance and prevention strategies for NTD in many LMIC.43 Availability and access to ETOPFA influence the live birth prevalence of NTD, but not all countries have legalized elective termination procedures when a pregnancy is diagnosed with fetal anomalies.24 Countries without ETOPFA services have a higher prevalence of live born babies with NTD.7,29 Reluctance to report ETOPFA, especially in countries where it is illegal, undercounts NTD prevalence.

Data considerations for estimation of global prevalence of NTD

Data considerations for estimation of global prevalence of NTD include selection of source population, surveillance methods, case classification, isolated versus multiple defects, severity of the defect, diagnostic specificity, prenatal screening, categorizing and counting multiple and duplicate occurrences, including all birth outcomes in the numerator and possibly in the denominator (live births, still births, and ETOPFA), providing confidence intervals around prevalence estimates to denote their precision, and reporting the prevalence stratified by important maternal and infant factors. Correct classification of birth outcome is integral when there is a live birth, or an early neonatal death with NTD. In a systematic review of prevalence studies in India, data quality was dependent on the structural organization of the health system, funding, availability of dedicated and trained staff, periodic data quality assessment, and monitoring.26 The WHO/CDC/ICBDSR birth defects surveillance manual provides a detailed guide to surveillance program managers for building, or integrating into an existing surveillance system, steps to positively influence data quality.44 These guidelines mainly call for implementation of standard surveillance protocols and tracking methods using multiple resources, use of valid case definitions and diagnostic classifications, electronic recording, and inclusion of all pregnancy outcomes. Ideally, it would be beneficial to have health services that cover all the population in a country or a region, which would then feed into developing a

Figure 2. Distribution of population-based frequency of neural tube defect by pregnancy outcome, Canada 1993–2002. Data from De Wals et al.33
robust surveillance system for NTD. But most LMIC lack universal access to healthcare. The components needed for comprehensive assessment of prevalence of NTD would have to stem from a good health care system, and development of such a system can be made into a priority among countries that lack them. The surveillance system should include live births, stillbirths, and ETOPFA after confirmative prenatal diagnosis of NTD. EUROCAT estimates that up to 80% of affected pregnancies in its network are terminated. Without examining all pregnancy outcomes, we introduce a major bias in prevalence estimation. A robust prevalence estimation procedure allows us to understand acute variations triggered by specific events, study the effect of prevention programs, analyze long-term trends, and improve comparability between studies.

**Significance of numerator and denominator in global NTD prevalence estimation**

The choice of numerator and denominator plays an integral part in estimating the true prevalence of NTD. Figures 1 and 2, using data from Ireland and Canada, respectively, show the effect of not counting stillbirths and ETOPFA in prevalence estimation, as surveying live births alone can underestimate overall prevalence by at least 50%. NTD outcomes in a country are largely based on prenatal screening programs and access to an elective termination when a fetal anomaly is diagnosed, as shown in Figure 3. Table 1 provides an overview of pregnancy outcomes for spina bifida, using 2012 data from various national or regional population- or hospital-based birth defects surveillance programs contributing to the ICBDSR, and the variation in spina bifida prevalence by pregnancy outcome (available at http://www.icbdsr.org/wp-content/annual_report/Report2014.pdf; Accessed on August 18, 2017).

**Discussion**

The current scant and fragmented surveillance data hinder our ability to adequately determine the global prevalence of NTD. Population-based active surveillance registries that track live births, stillbirths, and ETOPFA, using multiple sources of case ascertainment, would assist in our knowledge of the burden.
Table 1. Birth-defects registry-based estimates of live birth, birth, and stillbirth and total prevalence (per 1000) of spina bifida in ICBDSR programs worldwide, surveillance year 2012

| Country                  | Type of surveillance | Surveillance region | Total live births | Total stillbirths | Total ETOPFA | SB cases live births | SB cases stillbirths | SB cases ETOPFA | Life birth prevalence | Birth prevalence | Stillbirth prevalence | Total prevalence |
|--------------------------|----------------------|---------------------|-------------------|------------------|--------------|---------------------|---------------------|-------------------|----------------------|-----------------|---------------------|------------------|
| Argentina-RENAC         | HB                   | National            | 237,728           | 2243             | NP           | 114                 | 7                  | –                 | 0.48                 | 0.90            | 0.03                | –                |
| Australia-WARDA         | PB                   | Statewide           | 33,862            | 237              | 224          | 3                   | 0                  | 13                | 0.09                 | 0.09            | 0.00                | 0.47             |
| Canada-Alberta-ACASS    | PB                   | Provincial          | 51,994            | 324              | 122          | 18                  | 4                  | 0                 | 0.35                 | 0.42            | 0.08                | 0.42             |
| Canada-National-CCASS   | PB                   | National            | 287,667           | 2206             | P, NR        | 77                  | 19                 | –                 | 0.27                 | 0.33            | 0.07                | –                |
| Costa Rica-CREC         | PB                   | National            | 73,326            | 465              | NP           | 29                  | 0                  | –                 | 0.40                 | 0.39            | 0.00                | –                |
| Czech Republic          | PB                   | National            | 108,567           | 379              | 970          | 11                  | 0                  | 36                | 0.10                 | 0.10            | 0.00                | 0.43             |
| France-Paris            | PB                   | Regional            | 25,858            | 11               | 896          | 3                   | 0                  | 12                | 0.12                 | 0.12            | 0.00                | 0.56             |
| France-RYVEREA          | PB                   | Regional            | 65,447            | 649              | 532          | 14                  | 1                  | 23                | 0.22                 | 0.23            | 0.02                | 0.59             |
| Germany-Saxony-Anhalt   | PB                   | Federal state       | 16,888            | 63               | 76           | 1                   | 0                  | 11                | 0.06                 | 0.06            | 0.00                | 0.70             |
| Hungary                  | PB                   | National            | 90,269            | 16,450           | NR/NA        | 33                  | 0                  | 4                 | 0.37                 | 0.31            | 0.00                | –                |
| Iran-TROCA               | HB                   | Regional            | 6093              | 38               | P*           | 2                   | NR/NA              | NR/NA             | 0.33                 | –               | –                   | –                |
| Italy-Lombardy          | PB                   | Regional            | 7928              | 11               | 73           | 0                   | 0                  | 4                 | 0.00                 | 0.00            | 0.00                | 0.50             |
| Italy-Tuscany           | PB                   | Regional            | 29,934            | 81               | 188          | 0                   | 0                  | 5                 | 0.00                 | 0.00            | 0.00                | 0.17             |
| Japan                    | HB                   | National            | 107,481           | 606              | P, NR        | 50                  | 6                  | –                 | 0.47                 | 0.52            | 0.06                | –                |
| Mexico-RYVEMCE          | HB                   | National            | 13,803            | 204              | NP           | 11                  | 0                  | –                 | 0.80                 | 0.79            | 0.00                | –                |
| Mexico-NuevoLeon        | PB                   | Regional            | 70,531            | 461              | NP           | 29                  | 0                  | –                 | 0.41                 | 0.41            | 0.00                | –                |
| New Zealand              | PB                   | National            | 61,178            | 390              | NR/NA        | 4                   | NR/NA              | NR/NA             | 0.07                 | –               | –                   | –                |
| NorthernNetherlands      | PB                   | Regional            | 16,512            | 70               | 70           | 2                   | 0                  | 5                 | 0.12                 | 0.12            | 0.00                | 0.42             |
| Slovak Republic         | PB                   | Regional            | 55,535            | 180              | 0            | 10                  | 0                  | 0                 | 0.18                 | 0.18            | 0.00                | 0.18             |
| South America-ECLAMC     | HB                   | Multinational       | 91,221            | 1206             | NP           | 70                  | 4                  | –                 | 0.77                 | 0.80            | 0.04                | –                |
| Spain-ECEMC              | HB                   | National            | 83,963            | 272              | NR           | 2                   | 0                  | –                 | 0.02                 | 0.02            | 0.00                | –                |
| Ukraine-OMNI-Net        | PB                   | Regional            | 33,263            | 179              | P*           | 14                  | 0                  | 15                | 0.42                 | 0.42            | 0.00                | –                |
| UK Wales                 | PB                   | Regional            | 35,238            | 181              | 157          | 9                   | 1                  | 12                | 0.26                 | 0.28            | 0.03                | 0.62             |
| USA-Atlanta              | PB                   | Local               | 49,220            | 479              | 140          | 11                  | 4                  | 9                 | 0.22                 | 0.30            | 0.08                | 0.48             |
| USA-Arkansas            | PB                   | Statewide           | 38,217            | 283              | 9            | 13                  | 0                  | 2                 | 0.34                 | 0.34            | 0.00                | 0.39             |
| USA-Texas               | PB                   | Statewide           | 377,336           | 2087             | 167          | 153                 | 7                  | 4                 | 0.41                 | 0.42            | 0.02                | 0.43             |
| USA-Utah                | PB                   | Statewide           | 51,439            | 301              | 31           | 15                  | 1                  | 2                 | 0.29                 | 0.31            | 0.02                | 0.35             |

Data source: http://www.icbdsr.org/wp-content/annual_report/Report2014.pdf.

Abbreviations: ACASS, Alberta Congenital Anomalies Surveillance System; CCASS, Canadian Congenital Anomalies Surveillance System; HB, hospital based; CREC, Costa Rican Birth Defects Register Centre; ECEMC, Spanish Collaborative Study of Congenital Malformations; ECLAMC, Latin American Collaborative Study of Congenital Malformations; NA, data not available; NP, not permitted; NR, not reported; OMNI-Net, Ukraine Birth Defects Program; PB, population based; P, permitted; P*, ETOPFA permitted by reported only for selected malformations; REMERA, Registre des Malformations en Rhône Alpes; RENAC, National Registry of Congenital Anomalies of Argentina; RYVEMCE, Mexican Registry and Epidemiological Surveillance of External Congenital Malformations; SB, spina bifida; TROCA, Tabriz Registry of Congenital Anomalies; UK, United Kingdom; USA, United States of America; WARDA, Western Australian Register of Developmental Anomalies.

of NTD worldwide. Studies thus far have used modeled data to estimate a global prevalence of NTD. Blencowe et al. estimated the global prevalence of NTD in year 2015 while accounting for challenges discussed in our review, examining live and stillbirths and providing uncertainty intervals around prevalence estimates.6 Historic prevalence estimates of NTD in countries using robust population-based surveillance, before the availability of services for ETOPFA and before the implementation of mandatory folic acid fortification programs, could inform present day NTD burden in countries with similar characteristics but without surveillance systems.

RBC folate concentrations can also serve as biomarkers to predict the prevalence of NTD. Daly et al. first reported that low maternal RBC folate
concentrations during early pregnancy were associated with an increased risk of NTD in the offspring. The US–China Collaborative Community Prevention Project in China provided further support for the role of RBC folates in predicting the risk of NTD using data from a robust population-based study. In 2014, using data from the China study, Crider et al. published an optimal RBC folate concentration among women of reproductive age that serves as a threshold at which we can prevent NTD. The risk of NTD exhibits a dose–response effect and is highest at RBC folate concentrations lower than 1000 nmol/L. With this novel understanding, RBC folate concentrations can be utilized as a biomarker to predict the prevalence of NTD in the population and identify vulnerable groups. Biomarker analysis is timely and economical as countries strive toward establishing functional population-based birth defects surveillance systems. Recently, a study in Guatemala applied RBC folate analysis and estimated the NTD prevalence to be 1.4 per 1000 live births, with a geographic disparity ranging between 1.1 and 2.6 per 1000 live births.

In the last two decades, several countries have implemented robust surveillance systems to track NTD-affected pregnancies, and several have also invested in successful national-level interventions that improved folate status among women of reproductive age. However, most LMIC have lagged in undertaking surveillance and folic acid fortification programs owing to economic or systematic challenges and continue to have a high burden of NTD and associated adverse perinatal and child mortality.

To have reliable global NTD prevalence estimates, countries should invest in surveillance of birth defects. LMIC play an integral role in the process. Countries with hospital-based surveillance systems can scale up to a more comprehensive population-based system in a step-wise approach. Integrating community-based approaches to track home births and linking multiple data sources to collect comprehensive information on all pregnancies outcomes will address current gaps in data from LMIC. An alternate or parallel approach would be to conduct biomarker surveillance among women of reproductive age and model NTD burden on the basis of mean RBC folate concentrations. The goal should be to establish population-based birth defects surveillance systems that examine all pregnancy outcomes (including live births, stillbirths, and ETOPFA) as they yield total prevalence of NTD in a country, subsequently informing total global prevalence estimates. There is a need and missed opportunity to bring awareness about NTD as a global preventable child health and mortality issue, and this can be achieved with improved measurement of prevalence and implementation of proven and cost-effective interventions like mandatory fortification with folic acid. Global NTD prevalence data can drive political will and accelerate the implementation and evaluation of NTD prevention programs. With appropriate resources, political will, and commitment from countries, global NTD surveillance and prevention is an achievable goal.

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**Competing interest**

The authors declare no competing interests.
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