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Estimates of global and regional prevalence of neural tube defects for 2015: a systematic analysis

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Neural tube defects (NTDs) are associated with substantial mortality, morbidity, disability, and psychological and economic costs. Many are preventable with folic acid, and access to appropriate services for those affected can improve survival and quality of life. We used a compartmental model to estimate global and regional birth prevalence of NTDs (live births, stillbirths, and elective terminations of pregnancy) and subsequent under-5 mortality. Data were identified through web-based reviews of birth defect registry databases and systematic literature reviews. Meta-analyses were undertaken where appropriate. For 2015, our model estimated 260,100 (uncertainty interval (UI): 213,800–322,000) NTD-affected birth outcomes worldwide (prevalence 18.6 (15.3–23.0)/10,000 live births). Approximately 50% of cases were elective terminations of pregnancy for fetal anomalies (UI: 59,300 (47,900–74,500)) or stillbirths (57,800 (UI: 35,000–88,600)). Of NTD-affected live births, 117,900 (∼75%) (UI: 105,500–186,600) resulted in under-5 deaths. Our systematic review showed a paucity of high-quality data in the regions of the world with the highest burden. Despite knowledge about prevention, NTDs remain highly prevalent worldwide. Lack of surveillance and incomplete ascertainment of affected pregnancies make NTDs invisible to policy makers. Improved surveillance of all adverse outcomes is needed to improve the robustness of total NTD prevalence estimation, evaluate effectiveness of prevention through folic acid fortification, and improve outcomes through care and rehabilitation.

Keywords: estimates; mortality; neural tube defects; prevalence; spina bifida

Introduction

Neural tube defects (NTDs) are a group of severe congenital disorders associated with substantial mortality, morbidity, long-term disability, and psychological and economic costs.[1] Many NTDs are preventable with folic acid,[2–4] and long-term survival and quality of life among those living with NTDs can be improved through access to appropriate clinical care and rehabilitative services.[5–7] However, efforts for primary prevention and addressing the needs of those living with NTD have been hampered by a lack of transparent prevalence estimates to quantify the burden, especially in resource-poor settings. The Modell Database of Congenital Disorders (MGDb) was developed recently to estimate the birth prevalence of congenital disorders globally.[8,9] Previous global estimates using this method were published in the March of Dimes Global Report on Birth Defects.[10] These provided an estimate of 323,900 live births with NTDs in 2001; however, neither detailed methodology nor uncertainty estimates were provided.[10] Here, we build on the Modell methodology to generate current global and regional prevalence estimates for NTDs, with uncertainty intervals (UIs), for the year 2015 using updated input parameters.

Data to inform the prevalence of NTD are available from a number of sources, including population- and hospital-based birth defect surveillance registries; multicenter birth defects monitoring networks, such as the European

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Surveillance of Congenital Anomalies and Twins (EUROCAT),[11] the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR),[12] the Latin American Collaborative Study of Congenital Malformations (ECLAMC),[13] the National Birth Defects Prevention Network (NBDPN),[14] and the World Health Organization (WHO) South-East Asia Region's Newborn and Birth Defects Database (SEAR-NBBD);[15] individual hospital-based registration systems; and research studies (including hospital-based studies and household surveys). There are substantial differences in prevalence estimates based on sources of data and surveillance methodology. Ideally, a population-based surveillance system with clear case definitions and a defined geographical catchment area and including all pregnancy outcomes would yield the most complete estimate of NTD prevalence. However, such systems are lacking in all countries, with even the most comprehensive systems failing to capture spontaneous miscarriages and early fetal losses, where detailed investigation is rarely undertaken. Thus, we consider only measurable birth outcomes (live births, stillbirths, and elective terminations of pregnancy for NTDs).

The accuracy of surveillance methods can have significant effects on prevalence. Systems that include prenatal ascertainment and survey multiple data sources for documentation and triangulation of birth defects identify a greater number of cases compared with systems that track live births alone and rely on a single data source.[16] Incorrect documentation of birth outcomes and diagnosis of birth defects result in misclassifications between stillbirths and live births and isolated versus multiple defects (especially in stillbirths or early neonatal deaths without autopsies). Prevalence is largely under-ascertained and is highly variable, particularly in low- and middle-income countries (LMICs) without a capacity to use multiple data sources and limited tracking of elective termination of pregnancy for fetal impairment (eTOPFA) and stillbirths due to legislative or cultural barriers.

Apart from methodological influences, the estimated prevalence of NTDs can be influenced in populations by underlying risks due to genetic (such as *MTHFR* mutations among women of specific race and ethnicity), environmental, and nutrition differences,[17–19] as well as factors such as access to diagnostic services.[20]

To date, there has not been a standard approach for estimating NTD prevalence and presenting global and regional estimates. Different studies and registries use different approaches. The numerators in prevalence estimation generally include live births, and where possible stillbirths and eTOPFAs. For denominators, the most common approach is to use live births, with some countries including stillbirths where data are available. The correct denominator would include live births, stillbirths, and eTOPFAs; however, the overall frequency of stillbirths and eTOPFAs in the population is relatively small compared with overall live births, and their omission will have minimal effect on the prevalence estimate. As neither estimates of prevalence of eTOPFA or stillbirths $\geq$20 weeks are available for the majority of countries, using an approach similar to that taken for maternal mortality,[21] we included only live births in the denominator.

Here, we describe available data and generate regional and global estimates of the prevalence of NTD-affected birth outcomes and associated under-5 mortality for the year 2015. The prevalence estimates include only observed NTD birth outcomes, including live births, stillbirths, and eTOPFAs. Challenges in tracking pregnancies and the consequent paucity of data make it impossible to estimate NTD-associated early fetal losses and miscarriages. These estimates therefore represent an underestimate of the total number of NTD-affected pregnancies.

Methods

We sought to include as many available data sources as possible: (1) birth defect registries and (2) published literature. We undertook premodeling adjustments where necessary, seeking to improve data comparability between countries. The estimates are reported using the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER)[22] (see Appendix S1, online only).

Case definition

NTD-affected pregnancy is a pregnancy where the fetus is affected by one or more of the three major subgroups of NTDs: anencephaly, spina bifida, or encephalocele. NTD-affected pregnancies can result in one of four outcomes: (1) an early fetal loss or miscarriage (defined as a spontaneous pregnancy loss at $<$20 completed weeks of gestation), (2) a fetal death or stillbirth (a spontaneous pregnancy loss at $\geq$20

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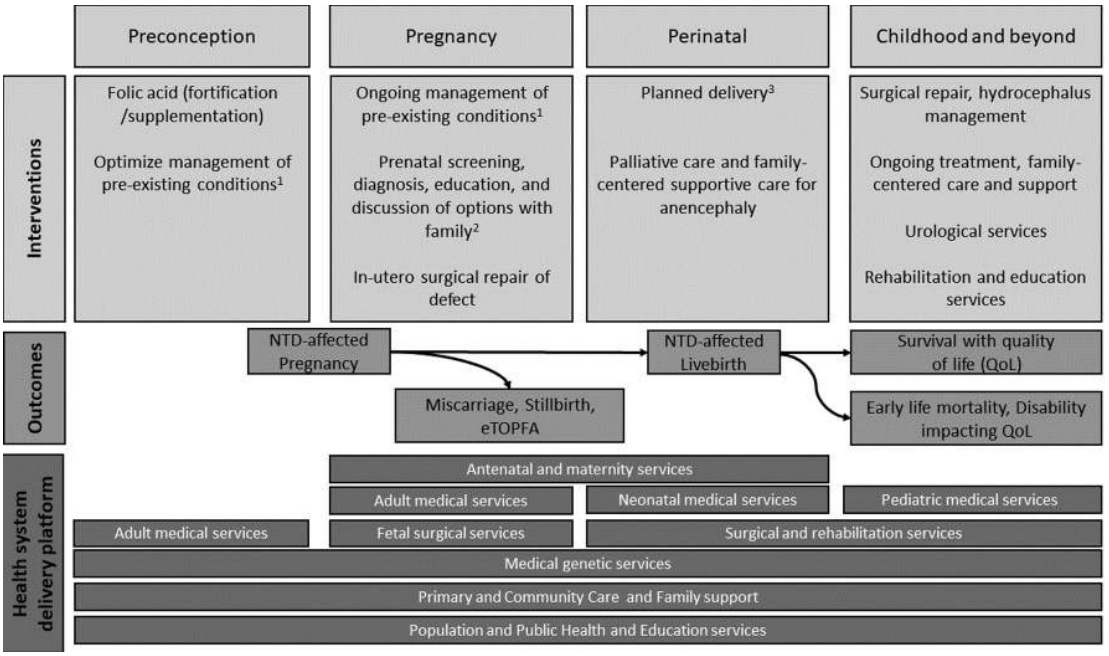

Figure 1. **Overview of interventions for and outcomes of neural tube defect–affected pregnancies. Adapted from Blencowe, *et al.*[28] [1]Including maximizing the control and appropriate medications for chronic conditions, including epilepsy and diabetes, with preconception optimization of medication to reduce risk. [2]Including information on eTOPFAs where they are legal and where it is the parental choice, prognosis and long-term outcomes, and plans for delivery. [3]Including delivery in a hospital with neonatal intensive care/neonatal surgical capabilities, planned cesarean section if required.**

completed weeks of gestation), (3) eTOPFA, or (4) an affected live birth. Figure 1 presents an overview of the possible outcomes of NTD-affected pregnancies and the interventions that can affect both the prevalence and the outcomes of these conditions. For this analysis, we considered in the numerator all NTD-affected pregnancy outcomes at ≥20 completed weeks of gestation and eTOPFAs at any gestation. Estimates of NTD-affected early fetal losses are not clearly possible. Data were also analyzed for the three major subgroups of NTDs. The term "birth outcomes" is used to refer to live births, stillbirths at ≥20 completed weeks of gestation, and elective terminations of pregnancy for NTDs at any gestation.

Prevalence data search: methodology

Birth defect registries. A web-based review of all available birth defect registry databases and multicenter birth defects monitoring networks (including EUROCAT, ICBDSR, ECLAMC, NBDPN, and SEAR-NBBD) was undertaken in March 2017. Data from all available registries for all years since 2000 were abstracted from each data source onto a standard abstraction form. Data were available for all years from most of these sources; therefore, to ensure that only the most recent data were used to inform the 2015 estimate, only data from 2005 onward were included (Appendix S2, online only). Country-specific data were included if they reported at least live birth and stillbirth outcomes for at least one subgroup of NTDs for at least a consecutive 5-year period since 2005. Inconsistent data or data with more than 50% of values missing were excluded.

Published literature review. To inform estimates for countries outside high-income country regions without recent, reliable, and population-based birth defect registry data on NTD birth prevalence, a literature review of published studies was undertaken. The review sought to include publications with data collection after 2000. Three recent systematic reviews summarized the available data on birth prevalence of one or more subgroups of NTDs in LMICs (Table 1).[23–25] Though each of these applied different inclusion criteria, overall they provided a comprehensive review of the literature, and it was

Table 1. Previous systematic reviews of birth prevalence of neural tube defects

Reference	Title	Inclusion criteria	Search dates
Lo *et al.*[23]	Estimating the burden of NTDs in LMICs	Population- or hospital-based studies reporting the prevalence of NTDs in LMIC context.	January 2000–February 2013
Zaganjor *et al.*[24]	Describing the prevalence of NTDs worldwide	Case–control and cross-sectional studies and reports with either a reported prevalence of NTDs (anencephaly/spina bifida/encephalocele) or numerator and denominator data allowing it to be calculated. Population ≥5000. Data collection 1990 or later. Excluded studies only reporting anencephaly and/or encephaloceles or using other NTD definitions; data from populations following a contamination event, case reports, and supplementation trials.	January 1990–July 2014
Atta *et al.*[25]	Global birth prevalence of spina bifida by folic acid fortification status	Original research with data collection since 1985. Population-based only (all cases in a defined geographic area or ascertainment from multiple hospitals or the only hospital in a defined area). Reported an incidence or prevalence estimate or cases of spina bifida per population denominator.	January 1985–December 2010

NTDs, neural tube defects; LMICs, low- and middle-income countries.

assumed that these search strategies captured all relevant published studies relating to NTD prevalence in LMICs. All studies included in these three reviews were screened for eligibility. In addition, an updated systematic review was undertaken covering January 1, 2013–March 17, 2017 to identify new publications appearing after the dates of the aforementioned systematic reviews. These searches were undertaken using the PubMed, Medline, EMBASE, and Global Health Library databases. Search terms used included "neural tube defects," "prevalence," and "developing countries" (including individual LMIC names) (Appendix S3, online only). Full-text review of the reference lists of all studies was undertaken to identify any further potential studies with NTD birth prevalence data.

The systematic review for current analysis included (1) studies reporting on primary data with population-based surveillance designs; (2) hospital-based surveillance studies with a defined geographical catchment area; and (3) hospital-based studies reporting birth prevalence of NTD cases after year 2000. Sources reporting a birth prevalence of at least one subgroup of NTD among at least one of the birth outcomes or providing a numerator and denominator to allow the calculation of the birth prevalence were included. Studies not meeting inclusion criteria, duplicate studies, and studies from countries with alternative reliable population-based birth registry data were excluded from the systematic review (Appendix S3, online only).[26] A checklist validated by Hoy *et al.* was adapted to assess study quality. Data from referral hospitals including pre- or postnatally referred cases were excluded (Appendix S3, online only).

Prevalence data search: results

Birth defect registries. The web-based review of birth defect registry data retrieved recent NTD birth prevalence data from 44 countries. Birth defect registry data from 39 countries met inclusion criteria and were included in the input database and contributed to the regional meta-analyses as appropriate. Birth defect registry data from four countries were excluded. These included Ireland, where more complete data from the registry were published;[27] New Zealand and the Slovak Republic, where only data on NTD-affected live births were available;[12] and Iran, owing to substantial data quality concerns and missing outcomes for multiple years.[12]

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For the United States, where data were available for states with and without prenatal ascertainment, only data from states with prenatal ascertainment were included, as the latter have lower reported prevalence, which is likely to be attributable to lower case ascertainment and missing eTOPFA outcomes.[16] As NTDs are a relatively rare outcome, and hence subject to year-to-year variation in prevalence, pooled prevalence data across available years from 2005 to 2015 were used as inputs to the database. Data from 23 countries identified through these searches plus comprehensive published data from Ireland[27] were assessed as subject to minimal biases and likely to provide a representative estimate of NTD prevalence in the country. See Appendix S2 for further details and Appendix S3 for list of included data (online only).

Published literature review. The literature review retrieved a total of 654 published study titles. Of these, 128 studies were considered for analysis after removing duplicates, studies not relevant to NTD prevalence, and data from countries with reliable birth registry data. A further 98 studies were excluded on full text review, and seven studies added from the reference lists searches. In total, 37 studies from 23 countries were included in the input database (Appendix S3, online only).

Estimation of access to services

For countries without data, the proportion of women and infants with access to a comprehensive package of optimal services, including diagnostic and specialist services such as urology and padiatric surgery, was estimated using an approach previously developed for the Modell Global Database where access to services is estimated based on the current infant mortality rate (Appendix S4, online only).[8,28] As eTOPFAs for NTDs are affected not only by the availability of prenatal diagnosis by prenatal ultrasound scan but also by the legal status, national policy, and local clinical and cultural practices of eTOPFA in each country, an adapted approach was undertaken (Appendix S5, online only).[28,29] For countries with no observational data, we assumed that the comprehensive package of optimal services includes routine antenatal ultrasound screening for structural abnormalities. In countries for which birth registry data on eTOPFAs are available, reported rates are used. Where no data are available and eTOPFA is legal, we assume that the proportion of women identified through ultrasound screening opting for pregnancy termination will be the same as the average rates among women in Europe (Appendix S6, Table S6B, online only). In countries where eTOPFA is not legal, unless there is clear evidence of widespread practice of eTOPFA, it is assumed for the purpose of modeling that no eTOPFAs are undertaken (Appendix S5, online only).

Modeling approach

NTD birth prevalence was estimated using a compartmental model including four steps: (1) estimation of the overall envelope of prevalence of NTDs per 10,000 live births; (2) estimation of the prevalence of the three subgroups of NTDs per 10,000 live births; (3) estimation of the prevalence of each birth outcome by overall NTDs and by the three subgroups per 10,000 live births, and (4) estimation of under-5 child mortality from NTDs. All estimates were generated at a national level by applying the four steps of the compartmental model in sequence to the UN Population Division estimated live births to generate estimated numbers affected for the year 2015.[30] All results are presented at the regional level using the UN Sustainable Development Goals regional classification[31] and at the global level.

NTD prevalence was calculated as:

$$\text{NTD birth prevalence} = \frac{\text{affected live births} + \text{affected still births} + \text{eTOPFAs for NTDs}}{\text{live births}} \times 10{,}000$$

Premodeling adjustments

Some of the limitations of the available data include the lack of representativeness, differing surveillance methods, differing application of case definitions and classifications, and missing data for NTD subgroups or outcomes. All of these can affect case ascertainment and reported NTD prevalence. Although it is not possible to adjust for all data limitations, input data were adjusted before use for missing NTD subgroup, missing birth outcomes, and reporting of cases versus affected fetuses/infants, in order to increase comparability. Overall, 29 of the 76 data inputs (39 from birth registries and 37 from literature searches) required some premodeling adjustment (see Appendix S4 for full details of these adjustments, online only).

Meta-analysis of reported prevalence by region

Standard meta-analysis techniques with random effects were used to obtain summary estimates of the parameters and 95% confidence intervals where appropriate, including reported prevalence by region and under-5 case fatality rates (CFRs).

Uncertainty estimation

For NTD birth prevalence, uncertainty was estimated assuming a Poisson distribution. We estimated 95% uncertainty estimates for the proportion in each NTD subgroup or with each birth outcome assuming a binomial distribution.

For each step, uncertainty around the estimates was quantified by taking 1000 random draws of the input parameters assuming the Poisson or binomial distributions as above. Data were summed at the regional or global level for each draw, and the 2.5th and 97.5th percentiles of the resulting distributions were presented as the uncertainty range. No estimations of the uncertainty around the estimated number of live births or access to care assumptions were included.

All analyses were undertaken in Stata 14. All data inputs, statistical code, and results are available online (https://doi.org/10.17037/DATA.264).

Results

Step 1: estimation of the overall envelop of prevalence of NTDs per 10,000 live births

For countries with recent registry data meeting inclusion criteria ($n = 24$). Recent population-based birth registry data that met the inclusion criteria, with reported rates that were subject to minimal biases and likely to provide a representative estimate of NTD prevalence in the country, were available for 24 countries (Appendix S2, online only). These regional or national reported NTD prevalence estimates were deemed as the preferred input data to estimate rates. For countries with only regional and not national birth defect registry data, reported regional NTD prevalences were assumed to be representative of the whole country. Where more than one regional registry was available, data pooled at the country level were used as an input. Only data from Canada were adjusted to include estimated eTOPFA; all other data were used as reported.

For countries without recent registry data meeting inclusion criteria ($n = 171$). NTD prevalence was estimated based on a meta-analysis of available regional data meeting inclusion criteria. United Nations (UN) regions were pooled to create 10 regions (Table 2, Appendix S7, online only). Meta-analyses were undertaken separately for countries with and without widespread coverage of a mandatory folic acid fortification program, where appropriate. Widespread coverage was defined as over 70% of the rice or wheat/maize flour in the country being fortified, based on data compiled by the Food Fortification Initiative.[32] Meta-analyses were not undertaken by individual country, as no country had a large number of input data points.

Step 2: estimation of the prevalence of the three subgroups of NTDs per 10,000 live births

Twenty-three of the 24 countries with available recent birth registry data meeting our inclusion criteria had data on the proportion of NTDs in each subgroup. For these countries, the proportion of total NTD-affected pregnancies in each subgroup was used as reported.

For all other countries, the overall NTD burden was divided assuming the proportion of all NTDs with each subgroup diagnosis to be equal to the EUROCAT pooled rates (i.e., when not tracked, 38.7% of all three major NTD subgroups was assumed to be anencephaly, 49.2% spina bifida, and 12.1% encephalocele (Appendix S6, Table S6A, online only)).[11]

Step 3: estimation of the prevalence of each birth outcome by overall NTDs and by the three subgroups per 10,000 live births

Twenty-three of the 24 countries with recent birth registry data that met inclusion criteria reported each birth outcome in each subgroup. For these 23 countries, the reported prevalence and proportions in each subgroup for each outcome were applied to the estimated number of live births in that country in 2015[30] to produce prevalence estimates for the year 2015.

For all other countries, the proportion of each subgroup with a given outcome was estimated as follows. For populations where eTOPFA is legal or where there is evidence of widespread practice, we used EUROCAT pooled data to estimate outcomes for those with access to specialist services (Table 3, Appendix S6, Tables S6B and S6C, online only).[11] For populations where eTOPFA is not legal, we used

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Table 2. Regional meta-analysis of overall birth prevalence of neural tube defects

Region	Number of studies	Overall NTD birth prevalence per 10,000 live births	95% Confidence intervals
Australasia	1	12.10	10.45–13.94
Latin America and the Caribbean: with folic acid fortification	12	7.78	6.58–8.97
Latin America and the Caribbean: without folic acid fortification	1	22.89	18.01–28.69
Eastern Europe and Central Asia	6	9.92	7.6–12.24
Sub-Saharan Africa: with folic acid fortification[a]	1	9.95	7.26–13.30
Sub-Saharan Africa: without folic acid fortification	6	15.27	10.19–20.34
East Asia	9	19.44	15.46–23.41
Northern Africa and Western Asia[b]	9	17.45	13.56–21.34
Europe	17	8.63	6.80–10.47
Southeast Asia[c]	2	6.76	5.77–7.75
North America	NA	Both countries in region have data	
Southern Asia[d]	11	31.96	23.81–40.12

[a]Based on a single South African study.[1]
[b]Studies are highly heterogeneous. Pooled regional data regardless of folic fortification (see Appendix S6, online only).
[c]Likely underestimate: used pooled hospital-based data from SEARO Newborn and Birth Defects Database in estimates.[2]
[d]Iran is the only country in the region with high coverage of folic fortification; we assumed that South Africa postfortification rates apply.[1]

contemporary data from Ireland[27] for those with access to specialist services and historical data from the United Kingdom for those without access to specialist services (Table 3, Appendix S6, Table S6D, online only).[33–36]

The number of NTD-affected live births in each subgroup was estimated by subtracting the eTOPFA and stillbirths from the overall estimated NTD-affected pregnancies in each subgroup. The overall NTD birth outcomes were calculated as the sum of each relevant outcome for each subgroup (e.g., total NTD eTOPFA = (eTOPFA for anencephaly) + (eTOPFA for encephalocele) + (eTOPFA for spina bifida)). Overall NTD prevalence by outcome was estimated as the number of the subgroup NTDs with the relevant birth outcome divided by the number of live births in the population.

Step 4: estimation of under-5 child mortality from NTDs

The number of under-5 deaths in children with NTDs was estimated by applying under-5 CFRs to the estimated live births with NTDs by country. CFRs, by subgroup, were estimated separately for children with access to optimal care services in a lower mortality setting (background neonatal mortality rate (NMR) <10), with access to care services in a higher mortality setting (background NMR ≥10), or with no access to care or supportive care only. Supportive care was defined as no availability of surgical care and includes nursing care and antibiotics only.

A systematic review of the outcomes of NTDs to age 5 was undertaken. For anencephaly, all data sources in all settings confirmed a 100% CFR by age 1 month. For spina bifida and encephalocele, there was a paucity of data to inform case fatality parameters from all settings. On the basis of the findings of the review, the parameters shown in Table 4 were included in the model as the best estimate of CFR by subgroup under the three different scenarios (Table 4). See Appendix S8 (online only) for further details.

Overall summary of NTD prevalence and under-5 mortality

Overall, there were an estimated 260,100 (95% UI: 213,800–322,000) NTD-affected birth outcomes worldwide in 2015, excluding early spontaneous fetal losses, with a global prevalence of 18.6 per 10,000 live births (95% UI: 15.3–23.0 per 10,000 live births) (Table 5; Figs. 2 and 3). Of that total, 23% (59,300 (95% UI 47,900–74,500)) were estimated to be eTOPFA for NTDs. A similar number of NTD-affected pregnancies were estimated to result

Table 3. Percentage of birth outcome parameters used in the compartmental model

NTD subgroup	% Affected pregnancies resulting in eTOPFA[a]	% Stillbirths in continuing pregnancies: no access to eTOPFA	% Stillbirths in continuing pregnancies: with access to eTOPFA
Anencephaly	90.6% of those with access to eTOPFA	56.0%	56.0%
Encephalocoele	61.7% of those with access to eTOPFA	11.3% if NMR < 10 21.8% if NMR ≥ 10	3.6%
Spina bifida	73.8% of those with access to eTOPFA	11.3% if NMR < 10 21.8% if NMR ≥ 10	3.1%

eTOPFA, elective termination of pregnancy for fetal impairment; NMR, neonatal mortality rate.
[a]Only estimated if eTOPFA is legal or there is evidence of widespread practice (Appendix S5, online only).

in stillbirth (57,800 (95% UI: 35,000–88,600)). Asia and Africa had the highest prevalence of NTD-associated stillbirths, amounting to 85% of all NTD-associated stillbirths occurring globally. Of the estimated 143,200 (95% UI: 105,500–186,600) NTD-affected live births worldwide in 2015, around 80% (117,900 (95% UI: 81,100–148,500)) were estimated to die before reaching the age of 5 years, the majority of these in LMICs (Table 6).

Of the total estimated NTD-affected birth outcomes in 2015, nearly half (128,000 (95% UI: 98,100–165,600)) were estimated to be cases of spina bifida (Appendix S9, Table 9A, online only). The majority of spina bifida–affected birth outcomes worldwide were estimated to result in affected live-born infants. In 2015, an estimated 66,000 (95% UI: 45,900–85,000) under-5 child deaths were associated with spina bifida.

Encephalocele was less common, with an estimated 31,700 (95% UI: 24,700–41,600) affected birth outcomes worldwide in 2015 (Appendix S9, Table S9B, online only).

There were an estimated 100,600 (95% UI: 72,000–142,400) anencephaly-affected birth outcomes in 2015 (Table S8C). In just under a third of these (27,900 (95% UI: 19,900–40,100)), it is estimated that the pregnancy was terminated following prenatal diagnosis. The remainder of cases were estimated to result in stillbirth (36,800 (95% UI: 15,300–66,600)) or neonatal death soon after birth (35,800 (95% UI: 14,500–64,700)).

Discussion

In spite of knowledge of the role of folic acid in the prevention of NTDs for the last 30 years, NTDs are still highly prevalent worldwide in 2015, with an approximate 260,000 affected pregnancies, excluding early spontaneous fetal losses. The majority of these are preventable cases, and understanding the current burden can have an important impact on their prevention. In 2015, there were an estimated 117,900 NTD-associated under-5 deaths. Neonatal death is universal for those with anencephaly, regardless of the setting, and mortality for other NTDs remains high in many LMIC settings, even when there is access to care services.[37] A similar number of NTD-affected pregnancies (117,100) ended in stillbirth or eTOPFA. These women and their families are frequently faced with stigma, isolation, guilt, and grief, which are often hidden.[38]

Despite improved outcomes with surgical and supportive care in high-income countries, affected individuals have an elevated mortality risk and residual disabilities and morbidities compared with unaffected individuals, leading to high levels of healthcare requirements. The economic, social, and psychological costs of caring for the needs of an affected child are large.[39–41] For the affected individual, the consequences are lifelong and frequently under-recognized.[42–44] Most LMICs do not have adequate healthcare professionals or services to address the surgical and multidisciplinary needs of those born with NTDs.

For society, NTD-affected pregnancies incur high costs, in terms of both direct expenditure on healthcare for women and affected individuals and societal costs in terms of lost human capital.[45] These impacts can be mitigated, at least in part, and quantification of the estimated prevalence and associated under-5 mortality can bring this issue, previously often invisible, to the attention of policy makers to facilitate improved resources to address the issue, as has been seen with other recent global estimates.[46] Increasing investment in both public health and patient services can improve outcomes.

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Table 4. Percentage of under-5 mortality parameters used in the compartmental model

NTD subgroup	No care/supportive care only (uncertainty range)	Optimal care including surgery background NMR ≥10 (uncertainty range)	Optimal care including surgery background NMR <10 (uncertainty range)
Anencephaly	100%	100%	100%
Spina bifida	95% (90–100%)	46.7% (38.4–55.1%)	18.3% (11.5–25.1%)
Encephalocoele	95% (90–100%)	46.7% (38.4–55.1%)	27.9% (24.4–31.9%)

NMR, neonatal mortality rate.

First, many NTDs are preventable with improved maternal folate status. Although adequate intake of folic acid does not prevent 100% of cases, owing to other environmental and genetic factors that influence the risk of NTDs, studies have shown it to be an effective preventative strategy.[2] While there is strong evidence to support a positive effect of mandatory folic acid fortification on NTDs,[4,16,47] evidence suggests that folic acid supplementation is usually commenced too late, and voluntary fortification has little impact.[20,48] Advocacy and resources are required for more folate-sensitive NTDs to be prevented through universal food fortification, and also through targeting women at high risk, including those with a previous NTD-affected pregnancy or chronic conditions (e.g., epilepsy), to optimize prepregnancy folate status.[49]

Second, access to adequate health care, supportive care, rehabilitation, and educational services can improve outcomes. These include access to prenatal diagnosis and information to allow women and families, together with health professionals, to plan optimal care within the appropriate legal, cultural, and belief systems. These may include eTOPFA or planned timing and place of delivery and ongoing support for affected women and families, particularly after a pregnancy loss or bereavement. Postnatal services, including surgical services and ongoing urological, rehabilitation, education, and supportive services, can improve the quality of life for affected individuals and their families. In many settings, the comprehensive, multidisciplinary, intersectoral team required to provide this is frequently lacking. In LMICs, even when surgical services are present, substantial barriers limit their uptake; in one study in Zambia, these included geography, economics, transportation, attitudes of healthcare workers, and beliefs of the women.[50] The long-term prognosis and quality of life of the 20,900 survivors with spina bifida and 4300 with encephalocele to age 5 could be improved with better access to full supportive and rehabilitative care.

Limitations

A large limitation of this work is the paucity of high-quality surveillance or observational data, especially from LMICs, which have the highest burden of NTD as a function of maternal malnutrition. We made numerous assumptions to arrive at our modeled estimates. To improve data comparability, premodeling adjustments of the input data were undertaken where possible. However, not all data limitations could be addressed.

Many previous studies seeking to quantify NTD burden in specific settings have excluded eTOPFA and/or stillbirths from their analyses, and hence substantially underestimate the total burden. While we sought to estimate all NTD-affected pregnancies resulting in a live birth, fetal death at ≥20 weeks of gestation, or eTOPFA for NTDs regardless of gestational age, it was not possible to include estimates of early fetal losses/miscarriage due to paucity of data. These estimates therefore represent an underestimate of the total number of NTD-affected pregnancies.

For our analysis, the term "stillbirth" was used to describe all fetal deaths, regardless of the definition used. Where possible, consistent with the majority of birth defect registries, fetal deaths at ≥20 weeks of gestation were used. Older data sources and those from LMICs tended to use the ≥28 weeks definition; however, this is unlikely to have a major effect on the estimate, since the majority of NTD-affected stillbirths occur during the third trimester.

Where possible, we sought to use national or nationally representative population-based data; however, this was available for only a minority of countries. For countries with population-based surveillance data available at a subnational level only, we assumed that these data would be a better

Table 5. Estimated overall neural tube defect birth outcomes worldwide in 2015

UN subregion	Regional average prevalence per 10,000 live births (UR)	Number of NTD-affected birth outcomes (UR)	Regional average eTOPFAs for NTD prevalence per 10,000 live births (UR)	Number of eTOPFAs for NTDs (UR)	Regional average stillbirth prevalence per 10,000 live births (UR)	Number of NTD-related stillbirths (UR)	Regional average NTD live births per 10,000 live births (UR)	Number of NTD-affected live births (UR)
Australasia and Oceania	12.1 (8.5–15.7)	750 (530–980)	5.6 (4.7–6.4)	350 (290–400)	1.6 (0.7–2.8)	100 (40–180)	4.9 (2.7–7.2)	300 (170–450)
Latin America and the Caribbean	8.6 (3.6–13.7)	9500 (3900–15,000)	2.9 (1.2–5.1)	3200 (1300–5600)	0.7 (0.2–1.4)	790 (250–15,200)	5.0 (2.1–7.2)	5500 (2300–7900)
Eastern Europe and Central Asia	9.7 (6.6–12.9)	4800 (3300–6400)	5.5 (4.1–7.0)	2700 (2000–3500)	0.8 (0.4–1.6)	440 (190–780)	3.3 (2.0–4.7	1600 (1000–2400)
Sub-Saharan Africa	14.2 (8.0–24.0)	49,100 (27,700–83,100)	0.4 (0.2–0.6)	1300 (700–2200)	4.5 (2.2–8.3)	15,400 (700–28,700)	9.3 (5.0–16.0)	32,300 (17,400–55,300)
East Asia	19.4 (11.0–28.0)	36,800 (20,800–53,100)	14.3 (8.0–20.7)	27,000 (15,100–39,300)	0.6 (0.3–1.1)	1200 (500–2100)	4.6 (2.5–7.0)	8700 (4800–13,200)
Northern Africa and Western Asia	17.5 (9.8–25.6)	20,700 (11,600–30,400)	4.8 (2.5–6.9)	5700 (3000–8100)	2.8 (1.4–4.7)	3300 (1600–5500)	9.8 (5.9–14.9)	11,700 (7000–17,700)
Europe	9.6 (8.8–10.4)	4200 (3900–4600)	7.3 (6.7–7.9)	3200 (3000–3500)	0.2 (0.1–0.3)	90 (50–140)	2.0 (1.9–2.3)	910 (830–1020)
Southeast Asia	13.1 (6.0–20.0)	16,100 (7400–24,500)	1.4 (0.6–2.1)	1700 (800–2600)	2.7 (1.1–4.7)	3300 (1400–5800)	9.1 (4.3–14.0)	11,100 (5300–17,200)
North America	7.5 (7.1–7.8)	3100 (2900–3300)	5.3 (5.0–5.6)	2200 (2100–2300)	0.3 (0.1–0.4)	(60–150)	2.1 (1.9–2.2)	860 (900–920)
Southern Asia	31.2 (22.0–43.0)	115,000 (81,200–158,800)	3.2 (2.6–5.0)	11,800 (9500–18,600)	9.0 (4.9–14.3)	33,100 (18,200–52,700)	19.0 (12.5–27.1)	70,200 (46,200–100,000)
Worldwide	18.6 (15.3–23.0)	260,100 (213,800–322,000)	4.2 (3.4–5.3)	59,300 (47,900–74,500)	4.1 (2.5–6.3)	57,800 (35,000–88,600)	10.2 (7.5–13.4)	143,200 (105,500–186,600)

eTOPFA, elective termination of pregnancy for fetal impairment; UR, uncertainty range.
Note: Numbers may not add up because of rounding. Numbers in each cell are rounded to the nearest 10 for numbers <1000 and the nearest 100 for numbers ≥1000.

representation of the overall country rate than a pooled regional estimate. However, some countries have highly variable regional prevalence rates, reflecting variation in folate status of women.[51] For countries and regions without national or nationally representative high-quality population-based data, we included data from hospital-based surveillance systems. Hospital-based data may underestimate prevalence in settings where only the wealthy are able to access facility-based care or where registration is voluntary and overestimate prevalence in settings where data come from the tertiary hospital where all cases are referred. All studies assessed had a moderate-to-high risk of bias, particularly regarding their generalizability to the national population. We sought to minimize overestimation by excluding data including prenatally and postnatally referred cases from the literature review. This assessment was more challenging in the hospital-based registry data sources where detailed description was less available. Region-specific data were lacking from the South-East Asia region. For this region, we used initial data based on the newly established hospital-based SEAR-NBDD database. This represents an important step toward counting perinatal conditions and birth defects in the region. As further data collection is undertaken in the region, a full assessment of the validity and reliability, including case ascertainment and misclassification, should be undertaken, and future estimates updated accordingly.

The analysis sought to include an estimate of the number of eTOPFAs due to NTDs in 2015. In view of the limitations of the data highlighted above, several assumptions were required in this estimation. For countries with no observational data, we first estimated the proportion of the population with access to optimal specialist services, including timely antenatal ultrasound screening for structural abnormalities. In the absence of empirical data, this is based upon the assumptions detailed above. It is assumed that no eTOPFAs are undertaken where eTOPFA is illegal, unless documented evidence of widespread practice is available. However, it is possible that women may be accessing these services,

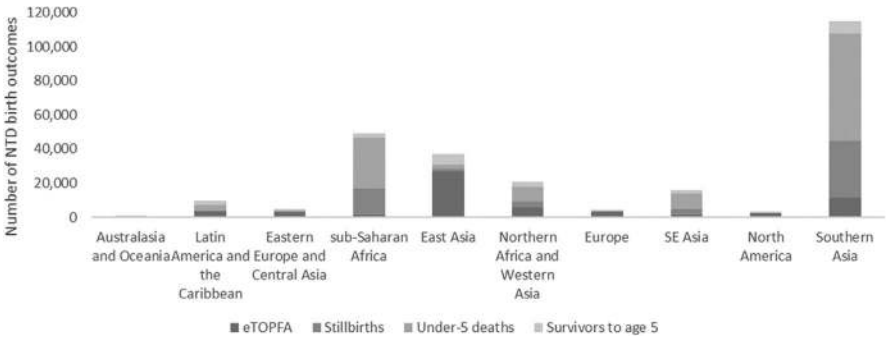

Figure 2. **Regional stacked bar chart showing the estimated number of NTD-affected birth outcomes.**

but no formal documentation is available; hence, eTOPFAs would be underestimated in these settings. For countries with no observational data and where eTOPFA is legal or its use is widespread, it is assumed that women will terminate affected pregnancies at the EUROCAT average rates. This may overestimate eTOPFAs for spina bifida in some regions, especially where the quality of ultrasound diagnosis is less robust, leading to fewer cases detected, or where eTOPFA, though legal, is less culturally accepted, or where geographical, financial, or other barriers limit access. Overestimation of eTOPFAs in these settings would not affect the overall estimated burden but would lead to underestimates of affected stillbirths, live births, affected individuals living with disability, and child deaths. Conversely, the assumption that no eTOPFA occurs in countries where eTOPFA is not legal is likely to underestimate eTOPFAs in those countries. In settings where termination of pregnancy is not legal, many women undergo illegal, unsafe abortions.[52] As routine prenatal ultrasound scanning becomes more widespread, more women with affected pregnancies may seek eTOPFA, regardless of its legal status.

Where data regarding the split by subgroup of NTDs were not available, we assumed that the EUROCAT average rates would apply. This approach was taken, as EUROCAT provides the most robust population-based data available. However, it has some limitations in that the distribution of the subgroups may vary according to nutritional, genetic, or other factors. Limited data are available to adequately quantify these differences, with a lack of high-quality population-based data with a low risk of bias from regions likely to differ most from Europe in terms of nutrition and genetic factors. Of the 37 included studies from low- or middle-income settings, only six populations from five studies presented data on the distribution of the subgroup of NTDs. These studies did not provide strong conclusive evidence to support the selection of a different subgroup distribution in these regions. As more robust population-based data become available from LMIC settings, this assumption should be reviewed.

These estimates use a compartmental model approach. We initially planned to model the overall prevalence of NTDs using linear regression with a random effect at the regional level, including dummy variables for study type, method of ascertainment, and coverage of folic acid food fortification. However, paucity of data—in particular suitable study and national predictor and covariate data—made this impossible.

In addition to providing a point estimate, we sought to quantify uncertainty around the estimates. Some account of uncertainty was included at each step of the compartmental model. However, our approach may underestimate uncertainty, as we were unable to capture uncertainty around the estimated number of live births in each country or around the access-to-care assumptions. In addition, while we assumed that the uncertainty around the reported prevalence would follow a Poisson distribution, this is likely to underestimate the uncertainty in many settings where underascertainment is a key concern.

Comparison with previous estimates

Previous estimates published in the March of Dimes Global Report on Birth Defects estimated a total

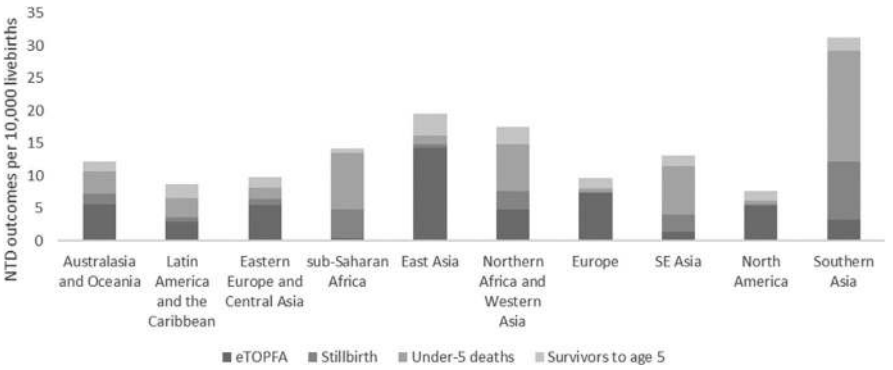

Figure 3. **Regional stacked bar chart showing the estimated prevalence for NTD birth outcomes per 10,000 live births.**

of 323,900 live births with NTDs in 2001.[10] These estimates for 2015 are slightly lower, reporting an overall birth prevalence, including eTOPFAs, stillbirths, and live births, of 260,100. While the detailed methods of the 2001 estimates have not been published, the differences could be accounted for by several factors. First, differences in estimates for China and other high-burden regions may be due to falling prevalence of folic acid–sensitive NTDs, due in part to the improved nutritional and folate status of women. Similar trends have been observed in the United Kingdom, where birth prevalence rates of over four per 1000 births in the 1950s in poor, working-class populations have fallen to the low rates reported in the present day.[36] Second, birth prevalence has fallen since 2001 in countries that have mandated and achieved high coverage of folic acid food fortification, as in most of North and South America. In addition, since 2001, prenatal detection of affected pregnancies has increased with widespread introduction of routine ultrasound during pregnancy, including fetal anomaly screening in all high-income and many middle-income countries. NTDs in general and anencephaly in particular can be relatively easily detected via ultrasound scan, and increased prenatal detection is likely to have increased the number of women and families seeking eTOPFAs where available, thereby reducing the number of affected live births. The Global Burden of Disease (GBD) includes NTDs as part of the 310 conditions estimated.[53] This approach produces estimates only for live births and only uses data from birth defect registries (43 countries); hence, no input data from high-burden regions (i.e., LMICs) are included. The GBD used a Bayesian modeling approach, seeking to adjust for underreporting and inclusion of stillbirths in reported prevalence within the modeling. The GBD reports overall prevalence in a population at all ages and mortality only among those born live, and hence the results are not directly comparable with these estimates.

A potential method of triangulation for the number of deaths is to compare these estimates to UN estimates for cause of under-5 deaths and reported vital registration data. We estimated that there were around 120,000 under-5 NTD-related deaths worldwide in 2015, compared with the UN's estimate of 558,554 under-5 deaths due to all congenital anomalies.[54] However, the UN-estimated number is recognized to underestimate these deaths with under-capture of these outcomes in both vital registration and verbal autopsy data owing to challenges in identifying nonvisible malformations (e.g., congenital heart defects) and to unwillingness of families to report birth defects because of stigma. In 2012 (the last year for which full data are available), a total of 3054 NTD deaths from 77 countries were reported to the WHO.[55] This number of reported NTD-related under-5 deaths is much lower than our modeled estimate, but this is not altogether surprising, as the highest burden countries do not have robust death registration systems to report causes of death to WHO, and the coverage of death registration is incomplete in many of these countries. However, when compared to reported numbers for North American, Latin American, and European regions, where most countries report cause of death, the reported number of deaths in 2012 is comparable to our estimate for 2015 (Appendix S10, online only).

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Table 6. Estimated number of NTD-related under-5 child mortality worldwide in 2015

UN subregion	Number of NTD-affected birth outcomes (UR)	Number of NTD-affected live births (UR)	Number of NTD-related under-5 deaths	NTD-related U5MR per 1000 live births[a]	Number of NTD survivors to age 5 (%)[b]
Australasia and Oceania	750 (530–980)	300 (170–450)	220 (100–300)	0.3 (0.2–0.5)	90 (30)
Latin America and the Caribbean	9500 (3900–15,000)	5500 (2300–7900)	3200 (1300–4500)	0.2 (0.1–0.4)	2300 (42)
Eastern Europe and Central Asia	4800 (3300–6400)	1600 (1000–2400)	860 (410–1300)	0.2 (0.1–0.3)	790 (49)
Sub-Saharan Africa	49,100 (27,700–83,100)	32,300 (17,400–55,300)	30,000 (15,700–49,900)	0.8 (0.5–1.4)	2300 (7)
East Asia	36,800 (20,800–53,100)	8700 (4800–13,200)	2400 (1300–3800)	0.1 (0.1–0.2)	6200 (71)
Northern Africa and Western Asia	20,700 (11,600–30,400)	11,700 (7000–17,700)	8600 (5000–12,900)	0.6 (0.4–1.1)	3100 (26)
Europe	4200 (3900–4600)	910 (830–1020)	240 (190–320)	0.1 (0.0–0.1)	670 (74)
Southeast Asia	16,100 (7400–24,500)	11,100 (5300–17,200)	9000 (4200–13,900)	0.6 (0.3–1.1)	2100 (19)
North America	3100 (2900–3300)	860 (900–920)	220 (150–280)	0.1 (0.0–0.1)	640 (74)
Southern Asia	115,000 (81,200–158,800)	70,200 (46,200–100,000)	63,200 (38,800–87,500)	1.7 (1.1–2.4)	7000 (10)
Worldwide	260,100 (213,800–322,000)	143,200 (105,500–186,600)	117,900 (81,100–148,500)	0.8 (0.6–1.1)	25,200 (18)

UR, uncertainty range.

Note: Numbers may not add up because of rounding. Numbers in each cell are rounded to the nearest 10 for numbers <1000 and the nearest 100 for numbers ≥1000.

[a]U5MR = under-5 mortality rate, presented here per 1000 live births to allow comparison with standard reporting of under-5 mortality.[3]

[b]Percentage survival is influenced by availability of prenatal diagnosis and uptake of elective termination of pregnancy for fetal impairment (eTOPFA). Regions with high rates of eTOPFA for anencephaly will have fewer live births with anencephaly, and therefore fewer neonatal deaths and higher survival rates overall for NTDs.

Conclusions

Overall, results from our systematic and meta-analyses show a high prevalence of NTDs globally, despite many being preventable before conception through mandatory fortification of staple foods with folic acid. This burden is largely hidden, with around half of all cases globally estimated to end in eTOPFAs or stillbirths, which are often hidden and invisible to policy makers. The impact of NTDs on mothers, families, and society is substantial. NTDs primarily affect women and families, confronting them with difficult decisions, including whether to continue with an affected pregnancy, creating psychological burdens following stillbirth or eTOPFA, and challenging them to finance and manage the complex care needs of an affected child.

Empirical data to inform both overall prevalence and each step of the estimation process are currently lacking, and these estimates therefore rely on several assumptions. Improving surveillance of all adverse birth outcomes, including live births, stillbirths, and eTOPFAs, through strengthened pregnancy and birth defect registries, especially in LMICs, is urgently needed to improve our understanding of total NTD prevalence. This will allow tracking of the effects of folic acid fortification on preventing affected pregnancies and of care on improving outcomes for affected births. Much of this burden is preventable before conception, and folic acid

intervention programs should be implemented alongside surveillance systems for achieving best results in monitoring and control of NTD prevalence and associated mortality.

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Supporting Information

Additional supporting information may be found in the online version of this article.

Appendix S1. GATHER checklist

Appendix S2. Registry data searches

Appendix S3. Study searches

Appendix S4. Methods for estimating access to care

Appendix S5. Status of TOP for fetal anomaly

Appendix S6. Premodeling adjustments

Appendix S7. Regional prevalence meta-analyses

Appendix S8. Under-5 mortality

Appendix S9. Regional results for neural tube defect subgroups

Appendix S10. Comparison with death certificate reporting

Competing interests

The authors declare that they have no competing interests.

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