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EDITORIAL

Teratology society position statement on surveillance and prevalence estimation of neural tube defects

In this position statement, the Teratology Society acknowledges the value of accurate measurement of total prevalence of neural tube defects (NTDs) in the population to support prevention, and advocates for rigorous surveillance worldwide. NTDs, include anencephaly and spina bifida and are some of the more common types of structural birth defects affecting pregnancies worldwide. They are easily identified both prenatally and at birth. Babies born with spina bifida face a high risk of mortality in early childhood and comorbidities throughout life; few babies with anencephaly are live born, and those who are die soon after birth. In addition, many anencephaly and spina bifida-affected pregnancies result in stillbirths or are electively terminated after prenatal diagnosis, depending on availability of prenatal diagnostic services and existing elective termination policies. Fortunately, a considerable number of NTDs can be prevented with maternal intake of 400 μg/day of folic acid before and during the first few weeks of pregnancy (CDC, 1992). Primary prevention of NTD via fortification of the food supply with folic acid is considered as one of the top 10 achievements in public health in the United States that occurred during 2001–2010 (CDC, 2011).

Birth defects surveillance is fundamental to understanding NTD prevalence and an essential aspect of prevention efforts. Active, multi-source, population-based birth defects surveillance with standard data collection protocols is vital to assess baseline NTD prevalence for an effective implementation of folic acid intervention in countries, and to evaluate its global impact. However, most developing countries, where the prevalence of NTDs tends to be the highest, lack surveillance systems (Zaganjor, Sekkarie, Tsang, et al., 2016); and the few systems that do exist in resource-poor settings are limited to tracking only live births, underestimating the total burden of NTDs (Blencowe, Kancherla, Moorthie, Darlison, & Modell, 2018; Christianson, Howson, & Modell, 2006).

The choice of pregnancy outcomes included in the numerator and denominator of the prevalence formula significantly influences the estimated burden of NTDs in the population. Lack of a standard approach in prevalence estimation is one of the most important limitations to understanding global burden of NTDs (Kancherla & Black, 2018). Methodologic approaches in prevalence estimation have differed across countries, with different pregnancy outcomes (i.e., live births, stillbirths, and elective terminations for fetal anomalies) used in the numerator and denominator of the prevalence formula. For example, years 2011–2015 surveillance data from the European Registry of Congenital Anomalies and Twins (EUROCAT) network of birth defects registries in Europe show that only 20% of NTD-affected pregnancies resulted in live births. The remaining pregnancies either resulted in stillbirths (4%), or were electively terminated prenatally after a diagnosis of fetal anomaly (76%) (EUROCAT, 2011–2015). In comparison to Europe where there is access to elective terminations for fetal anomalies, the proportion of stillbirths in developing countries without similar access, is estimated to be about 20% (Blencowe et al., 2018). Thus, limiting surveillance to live births alone will grossly underestimate the total prevalence of NTDs in the population.

Estimates of the global prevalence of NTDs using available data tend to result in underestimation of their true prevalence. Lack of robust country-specific birth defects surveillance data, especially in developing countries, limits our ability to estimate the global prevalence of NTDs (Modell et al., 2018). This leads to alternative methods, such as application of statistical models, to estimate prevalence. Few global prevalence models are based on robust data, and the assumptions used in these models are based primarily on data from developed countries. The Institute of Health Metrics and Evaluation publishes periodic Global Burden of Disease (GBD) estimates for NTDs (http://www.healthdata.org/). The 2010 GBD model for NTD prevalence was based on vital registration or verbal autopsy reports, which are known to be largely incomplete or undocumented in developing countries. Stillbirths, anencephaly, or NTDs with other co-occurring birth defects were not included in the prevalence estimation process. Thus, the initial GBD estimate of ~65,000 NTDs does not reflect the expected total prevalence of NTDs. Their estimate corresponds to a global NTD prevalence of 0.5 per 1,000 live births, which is very low relative to that shown in other studies. A more rigorous

model with country-specific NTD prevalence estimates was developed by Modell (Modell, Darlinson, Moorthie, et al., 2016). Due to the paucity of country-specific data on prevalence of birth defects, especially in low- and middle-income countries, Modell's model extrapolated data from several sources, and developed a pooled model for prevalence. These pooled estimates were reported as less precise, but allowed a general comparison of NTD prevalence across different countries. Recently, building on Modell's method, Blencowe et al. (2018) estimated 260,100 NTD-affected stillbirths and livebirths worldwide annually (95% uncertainty interval: 213,800–322,000), at a global prevalence of 1.9 per 1,000 live births (95% uncertainty interval: 0.8–3.1). This model suggested that developing countries had the highest prevalence of NTDs. Due to assumptions and limitations involved in the model, the researchers cautioned that their estimate could still be an undercount of total global prevalence of NTDs.

Unlike for other birth defects, primary prevention is possible for NTDs. The prevention is proven, effective, safe, economical, and feasible at a population scale through fortification of staple foods with folic acid (Atta, Fiest, Frolkis, et al., 2016; Castillo-Lancellotti, Tur, & Uauy, 2013; Rosenthal et al., 2014; Williams, Mai, Mulinare, et al., 2015). The effectiveness of interventions can be measured using accurate prevalence estimates from a population-based surveillance. Policy makers often seek information on prevalence of NTDs for allocating funds for prevention programs; however, inadequate surveillance or inaccurate modeling assumptions would yield prevalence estimates that are spuriously lower than the actual prevalence. Such underestimation could lead policy makers to undervalue the potential of establishing programs to prevent NTDs.

The Teratology Society recommends the following approaches for standardizing and improving NTD prevalence estimation globally:

- Prevalence estimates should be based on population-based surveillance that utilizes multiple data sources and standard data collection protocols to include all pregnancy outcomes and infant mortality. Importantly, for estimation of total prevalence of NTDs, case ascertainment should include all pregnancy outcomes: live births, stillbirths, and elective terminations of pregnancy for fetal anomalies. Prenatal ascertainment may not be possible in all countries, especially in resource-poor settings. In any setting, surveillance can aim at including all live births and fetal deaths, while also standardizing the age at gestation when surveillance can be initiated. In some countries, early neonatal deaths with co-occurring prematurity and NTDs are classified for prematurity but not birth defects, leading to underestimation of NTD prevalence. Such outcomes should be included to capture all NTDs.
- Prevalence estimates should capture all NTD phenotypes. Clinical inclusion and exclusion criteria are essential considerations when estimating the overall prevalence of NTDs. Anencephaly should be included. In addition, some NTDs co-occur with other major birth defects or syndromes; these cases should be included as well.

Resources exist to help build robust surveillance systems or to improve existing systems. The World Health Organization (WHO), National Center on Birth Defects and Developmental Disabilities from the United States Centers for Disease Control and Prevention (CDC), and the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) have developed a standard guide and training for entities or countries interested in conducting birth defects surveillance (see information at: http://www.who.int/nutrition/publications/birthdefects_manual/en/). The training offers participants an atlas of congenital anomalies for standardizing diagnosis and coding, and a facilitator's guide to help facilitators who provide training on birth defects surveillance (WHO/CDC/ICBDSR, 2014). On-the-ground technical expertise is available through CDC for initiating surveillance in developing countries. Countries intending to establish a population-based birth defects surveillance system (or to convert from a hospital-based surveillance system to one that is population-based) can utilize available tools (see information at: http://www.icbdsr.org/online-self-paced-course-on-birth-defect-surveillance-and-prevention/), and countries with existing surveillance systems can also use these tools to modify or improve their current protocols.

Partnerships are essential for birth defects surveillance. Local, national, and international collaborations enhance knowledge sharing. Collaborations can address gaps and are critical to lend a stronger voice for advocacy. The ICBDSR, EUROCAT, and the Latin American Collaborative Study of Congenital Malformations (ECLAMC) are examples of successful collaborative networks that conduct birth defects surveillance and influence prevention and care policies for NTDs in their respective regions. These collaborative networks follow standardized approaches in surveillance methods, and allow comparison of prevalence estimates between countries, pool information for research, and study trends overtime.

Equal involvement of community, local leadership, nongovernmental organization, and civil society organization is needed for sustaining surveillance efforts. Stakeholder involvement during different phases of surveillance can promote a sense of ownership, provide information on the political and medical landscape, and encourage buy-in from the community and local leaders. This community involvement can be especially advantageous for surveillance programs in resource-poor settings that lack adequate prenatal services, and where a majority of births occur at home. The

WHO/CDC/ICBDSR manual for establishing birth defects surveillance systems addresses such models to train local personnel assisting in conducting surveillance within countries. Designated members from local health facilities and local resources can also be enlisted to contribute to NTD surveillance.

The position on NTD surveillance by the Teratology Society aligns with that of other leading birth defects and public health organizations. The 63rd World Health Assembly resolution on birth defects has urged all member states to prioritize birth defects (WHO, 2010) and to "develop and strengthen registration and surveillance systems for birth defects within the framework of national health information systems in order to have accurate information available for taking decisions on prevention and control of these birth defects and to continue providing care and support to individuals affected by birth defects." A recent consensus statement published by attendees of the 7th International Conference on Birth Defects and Developmental Disabilities in Developing World stressed the need to establish surveillance systems and improve data quality (Darmstadt, Howson, Walraven, et al., 2016). Botto and Mastroiacovo (2018) proposed a novel concept of triple surveillance for NTDs, integrating surveillance of folate insufficiency, NTD prevalence, and health outcomes associated with NTDs. They state "By doing so, surveillance becomes not a roadblock but a preferential path to prevention and better care." In a 2014 resolution, the Teratology Society called for global total prevention of folic acid-preventable spina bifida and anencephaly by 2024 (Smith & Lau, 2015).

The Society supports accurate measurement of prevalence as an integral part of NTD prevention, and emphasizes that prevalence should reflect all NTDs regardless of birth outcome or phenotype. Surveillance data from developing countries are vital to estimate the true burden of NTDs in the population. The Society acknowledges that the main purpose of any surveillance program for NTDs should be for public health action, and hence inaccuracies in surveillance findings that have a potential to hinder prevention should be addressed and corrected as soon as possible. The society will continue to champion for improved NTD prevalence estimation procedures and standardizing them globally. NTD prevalence estimates derived from robust surveillance systems are preferable to modeled estimates. But, until all countries are capable of conducting NTD surveillance, there will be a degree of reliance on modeled estimates. The empirical data that currently inform these modeled estimates should be improved.

As stated by Blencowe et al. (2018) at the conclusion of their systematic analysis of global prevalence of NTDs, "The burden of NTD is largely hidden, with around half of all cases globally estimated to end in elective terminations or stillbirths, which are often hidden and invisible to policy makers." Ultimately, the validity of modeled NTD prevalence estimates derived from the Modell method or the Global Burden of Disease studies can be improved if more developing countries invest in surveillance as a public health measure of a preventable birth defect. The return on this investment would be high quality data available for policy makers to promote and evaluate prevention of NTDs. The Society calls for a collective effort by countries to make all NTDs visible, not just those that are easy to count.

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CONFLICT OF INTEREST

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