Neural Tube Defects and Folic Acid Food Fortification in Europe

Follow-up on: Atta CA, Fiest KM, Frolkis AD, et al. Global birth prevalence of spina bifida by folic acid fortification status: a systematic review and meta-analysis. Am J Public Health. *2016;106(1):e24–e34.*

Neural tube defects (NTDs) attributable to failure of the neural tube to close in early pregnancy include anencephaly and encephalocele, in which neonatal survival beyond the first week of life is rare, and spina bifida, in which neonatal survival is usually associated with serious lifelong clinical consequences. Worldwide, NTDs are the most common preventable major congenital anomaly.

SUPPLEMENTATION STRATEGY

A generation has passed since two European landmark randomized controlled trials found that folic acid (FA) supplementation started before pregnancy and continued until after closure of the neural tube prevented about two thirds of NTDs.[1] A maternal red blood cell folate greater than 906 nanomoles per liter has been associated with a decreased risk of a NTD, but few women, even those on a folate-rich diet, can achieve this level.[1] Since 1993, therefore, national guidelines worldwide have recommended that women who are capable of becoming pregnant should take oral FA supplementation for primary prevention. This approach was reaffirmed in 2017 by the US Preventive Services Task Force following a review of current evidence.[2] This public health strategy, however, has made little impact on the prevalence of NTDs. Compliance with supplementation before pregnancy is weak mainly because of inadequate maternal knowledge and high levels of unplanned pregnancies. The majority of women do not start FA until their pregnancy test is positive, which is usually around the time the neural tube closes.[3]

FOOD FORTIFICATION STRATEGY

Before 1998, FA fortification of food internationally was voluntary and highly variable. Since 1998, the United States has mandated fortification of enriched cereal grain products with 140 micrograms per 100 grams.[4] About 85 other countries have followed, particularly in the Americas. The evidence is that the prevalence of NTDs in the United States declined after mandatory fortification. Data from 19 population-based surveillance programs covering the years 1999 to 2011 reported a 28% reduction in NTDs, which meant that an estimated 1300 births with NTDs were averted annually after fortification.[4] It is estimated that primary prevention attributable to mandatory fortification led to annual savings in total direct costs of $508 million.[4]

The American strategy for primary prevention of NTDs has received further support from a systematic review by Atta et al., published in 2016. The authors examined 179 studies and provided a meta-analysis of 123 studies in English or French published between 1985 and 2010 that examined the prevalence of spina bifida alone.[5] The pooled spina bifida rate was 0.47 per 1000 live births, although case ascertainment, surveillance methods, and reporting varied across the population-based studies.

In studies including live births, stillbirths, and terminations, the prevalence of spina bifida was 0.35 per 1000 (95% confidence interval [CI] = 0.32, 0.39) in geographic regions with mandatory FA fortification compared with 0.52 per 1000 (95% CI = 0.46, 0.59) in regions with voluntary FA fortification.[5] The differences were similar if prevalence rates of spina bifida were confined to stillbirths. When pooled prevalence of spina bifida including live births, stillbirths, and terminations were analyzed by continent, the prevalence was 0.39 per 1000 (95% CI = 0.34, 0.44) in North America, which was low compared with 0.53 per 1000 (95% CI = 0.45, 0.61) in Europe. Limited data were available from other continents, resulting in wide confidence intervals.

EUROPEAN TRENDS

In Europe, most population-based congenital anomaly registers belong to the European Surveillance of Congenital Anomalies (EUROCAT) network with a common database. In a study supported by the European Commission, trends on the total prevalence and live birth prevalence of NTDs were assessed by using data on 11 353 cases not associated with chromosomal anomalies from 28 registries in 18 countries for the years 1991 to 2011.[6] Trends were examined for all NTDs combined as well as separately for anencephaly and spina bifida.

Overall, the pooled total prevalence was 0.91 per 1000 births and the prevalence in 2011 was comparable to that in 1991. The trend patterns for anencephaly and spina bifida were similar. Neither anomaly decreased over time. As a result of secondary prevention with prenatal diagnosis and termination of pregnancy, the live birth prevalence decreased over time, especially for anencephaly.

In Ireland, there was a long history of high rates of NTDs, which declined in the 1980s and 1990s.[7] In a comprehensive national audit in Ireland that used multiple sources, the overall rate was 1.04 per 1000 births in 225 998 total births between 2009 and 2011 with no evidence of any improvement in trends since the introduction of guidelines for supplementation in 1993. A similar audit for the four years 2012 to 2015 again confirmed the failure of NTD prevalence rates to fall nationally (verbal communication, Robert McDonnell, Ireland East Registry, 2018). A decision by the Irish government to introduce mandatory fortification in 1996 was deferred indefinitely two years later. Similar decisions on mandatory fortification have been made politically in the United Kingdom despite medical advice.

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TRANSATLANTIC DISPARITIES

In public health, global disparities are well established but are usually driven by socioeconomic factors. The disparity in NTD prevalence trends, however, between two well-resourced continents, Europe and North America, is striking. North America has successfully implemented a primary prevention policy with a twin strategy of voluntary supplementation and mandatory food fortification, as well as a secondary prevention policy with prenatal screening. By contrast, European countries have a similar supplementation strategy but have a greater dependence on secondary prevention because, to date, they have failed to implement mandatory fortification.[6]

IMPLEMENTATION OF MANDATORY FORTIFICATION

The implementation of mandatory FA fortification poses many challenges. Decisions have to be made about what foods should be fortified, at what level food should be fortified, how the quality of fortification should be monitored, how blood folate levels would be monitored (especially in vulnerable population groups), how NTD prevalence would be monitored, and how other possible clinical benefits or risks would be monitored.

As food and food ingredients increasingly cross national boundaries with globalization, FA food fortification in Europe will almost certainly require standardized legislation and regulation. After Brexit, this has become even more complicated and uncertain in the European Union. Will mandatory food fortification be standardized in the European Union? And will there be regulatory alignment with the United Kingdom? In Ireland, this is particularly problematic because most flour is milled in Scotland and then imported. Will future food regulations in Scotland be decided in London, England, or in Brussels, Belgium?

Mandatory fortification will increase costs for the food industry and will increase costs for regulatory bodies. However, if other continents can prioritize the needs of women and their babies, why can't Europe?

Europe needs to prioritize implementing mandatory FA food fortification because primary prevention is clinically preferable than the present overreliance on secondary prevention. It may also potentially be more cost-effective. AJPH

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REFERENCES

1. Chitayat D, Matsui D, Amitai Y, et al. Folic acid supplementation for pregnant women and those planning pregnancy: 2015 update. *J Clin Pharmacol*. 2016;56(2):170–175.

2. Viswanathan M, Treiman KA, Kish-Doto J, Middleton JC, Coker-Schwimmer EJ, Nicholson WK. Folic acid supplementation for the prevention of neural tube defects: an updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2017;317(2):190–203.

3. Cawley S, McCartney D, Woodside JV, et al. Optimization of folic acid supplementation in the prevention of neural tube defects. *J Public Health (Oxf)*. 2017; Epub ahead of print.

4. Williams J, Mai CT, Mulinare J, et al. Updated estimates of neural tube defects prevented by mandatory folic acid fortification—United States, 1995–2001. *MMWR Morb Mortal Wkly Rep*. 2015;64(1):1–5.

5. Atta CA, Fiest KM, Frolkis AD, et al. Global birth prevalence of spina bifida by folic acid fortification status: a systematic review and meta-analysis. *Am J Public Health*. 2016;106(1):e24–e34.

6. Khoshnood B, Loane M, de Walle H, et al. Long term trends in prevalence of neural tube defects in Europe: population based study. *BMJ*. 2015;351:h5949.

7. McDonnell R, Delany V, O'Mahony MT, Mullaney C, Lee B, Turner MJ. Neural tube defects in the Republic of Ireland in 2009–11. *J Public Health (Oxf)*. 2015;37(1):57–63.

Moving Beyond the Cause Constraint: A Public Health of Consequence, May 2018

See also Hernán, p. 616; Begg and March, p. 620; Ahern, p. 621; Chiolero, p. 622; Glymour and Hamad, p. 623; Jones and Schooling, p. 624; and Hernán, p. 625.

Both of us have been involved in decades' worth of population health science writing that has, at times, sidestepped the issue of whether a condition, factor, or circumstance of interest was indeed a "cause," sometimes nudged by coauthors, other times by editors, others by reviewers, and still others by our own timidity, as we sought to avoid unnecessary argument.

CAUSE AND CONSEQUENCE

It is this timidity that an excellent and provocative commentary in this month's *AJPH* by Hernàn (p. 616 and p. 625) seeks to dispel. Hernàn argues that we should use the word "cause" when we mean cause and persuasively and most provocatively outline the dangers that emerge when we avoid the word "cause." Several other articles in this issue (see Begg and March [p. 620], Ahern, Chiolero [p. 622], Glymour and Hamad [p. 623], and Jones and Schooling [p. 624]) elaborate on this.

When we focused on promoting a public health of consequence,[1] it was likely unintentional that our language and thinking returned to the notion of cause[2] in public health; to actually move the needle on population health, we have to move our thinking, our research, and our actions from describing disparities to understanding the causes of them. Reflecting on the arguments introduced by Hernàn, we wonder why "cause" has become such

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