Review of interventions for the prevention and control of folate and vitamin B\textsubscript{12} deficiencies

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Abstract

Folate and vitamin B\textsubscript{12} deficiencies represent important and evolving global health challenges that contribute to the global burden of anemia, neurologic conditions, neurodevelopmental disorders, and birth defects. We present a review of population-based programs designed to increase consumption of folates and vitamin B\textsubscript{12}.

A folic acid supplementation program targeting couples prior to marriage in China has led to optimal consumption of supplements containing folic acid and a significant reduction of neural tube defects (NTD). Supplementation programs that use mass community education show some promise, but have not been shown to be as effective as targeted education. The success of supplementation programs hinges on a strong and persistent educational component and access to the supplements.

Fortification with folic acid has been shown to reduce the prevalence of NTD in the countries where it has been implemented. Challenges to fortification programs include identifying the appropriate delivery vehicles, setting the optimal fortification level, sustaining the quality assurance of the fortification level, and addressing regulatory challenges and trade barriers of commercially fortified flours.

Supplementation and fortification are cost-effective and viable approaches to reducing the burden of folate deficiency. The experience with interventions involving folic acid could provide a model for the subsequent development of supplementation and fortification programs involving vitamin B\textsubscript{12}.

Key words: Folate, fortification, supplementation, vitamin B\textsubscript{12}

Introduction

In this report, we present a review of population-based approaches to increase folate and vitamin B\textsubscript{12} consumption. Although many examples of effective interventions involving folic acid are available, no published report that we are aware of addresses population-based interventions involving vitamin B\textsubscript{12}. Therefore, our review focuses on folic acid interventions and includes some surveys of folate status among different populations, community interventions related to folic acid, and surveys on the consumption of folic acid, as well as reports of NTD prevalence and serum and red blood cell folate before and after supplementation and fortification. In addition, our review emphasizes supplementation and fortification because there were no reports of population-based interventions involving dietary diversification to increase folic acid consumption. We believe that the experience available for folic acid might be useful for public health officials planning intervention programs for both folate and vitamin B\textsubscript{12} deficiencies.

Overview of interventions

Increasing a population’s consumption of folic acid can reduce the health burden of folate deficiency, but the challenge for public health officials is to determine what population-based approaches can be effective and affordable in their communities. Three general public health interventions directed at ensuring adequate folate status through improving intake are available: dietary diversification, supplementation, and fortification. Dietary diversification promotes increased consumption of folate-rich foods through education and facilitating community access to those products. Supplementation programs promote use of vitamin
supplements in the form of pills, powders, or other preparations to a target population. Fortification is based on adding the micronutrient of interest to a widely or universally consumed food vehicle of the target population. Approaches that focus on treating clinically evident folate and vitamin B12 deficiencies in individuals are not included here.

Dietary diversification attempts to ensure optimal nutrition through good dietary habits and is the basis for many health promotion and disease prevention efforts. Foods naturally rich in folate, such as fruits, green leafy vegetables, beans, and peas, are often a part of such efforts because they are also rich in other nutrients and can offer a variety of health benefits. All public health programs promoting optimal nutrition should include dietary diversification as a primary strategy. However, attaining a daily consumption level of 400 µg of folic acid among women of reproductive age for the purpose of preventing neural tube defects (NTD) is difficult to achieve through dietary sources alone, especially on a long-term basis, for several reasons: 1) compared with synthetic folic acid in supplements, naturally occurring folate is less bioavailable and less stable in heat and after prolonged cooking [1]; 2) populations in some areas of the world, especially in economically developing areas, might not have access to folate-rich foods throughout all seasons because of the lack of fresh produce; and 3) sustained, intensive education efforts are required to achieve and maintain effectiveness. In addition, dietary approaches can be too costly for some populations or individuals. They might, therefore, be limited in their effectiveness.

Effective dietary diversification and supplementation rely on a strong educational component, as well as increasing accessibility of foods and supplements in the target area. Fortification strategies require not only a suitable vehicle, but also regulatory or legislative action and strong partnerships with the private sector (which produces the target vehicles) to ensure compliance and a high level of uniformity in the end product. All strategies need an evaluation component that monitors changes in the consumption of folate and the health impact on the target population, such as a reduction of NTD. Evaluating the effects of education and changes in attitudes and knowledge about the importance of optimal consumption of folate is a very useful monitoring tool.

The supplementation approach to preventing NTD is based on targeting women of reproductive age before conception (particularly when they might be contemplating a pregnancy), and educating them about the benefits of consuming folic acid to prevent serious birth defects in a manner that leads to the desired action: daily consumption of a supplement containing the recommended amount of folic acid during the periconceptional period. This strategy might be useful in countries or areas where most pregnancies are intended and where it is possible to reach women prior to conception. In countries where nearly half or more of pregnancies are unintended, a supplementation approach is more difficult and costly because it would need to be targeted to all women of reproductive age. On the other hand, supplementation is the only strategy that can realistically provide a dose as high as 4,000 µg/day, the amount recommended to prevent recurrence in women with a prior history of a NTD-affected pregnancy [2]. Targeting women who are at risk for a recurrence might be best addressed in the context of the medical care system.

Fortification, the process of adding micronutrients to an appropriate food vehicle in order to prevent disease and correct community-wide deficiencies, represents a longstanding public health legacy that has effectively rid populations of serious conditions such as goiter, rickets, and pellagra [3–5]. This strategy involves identifying a fortification vehicle that is universally and consistently consumed by the target group in a population. The vehicle should be stable in storage, low in cost, acceptable in color and taste, and accessible to the target group. In some countries, foods such as cereal grain flour, milk, and salt are already being used as fortification vehicles for various micronutrients, and the existing fortification programs can be expanded to include folic acid without incurring substantial costs. In other countries, however, the cost of installing and maintaining the necessary equipment to fortify the vehicle and the training of workers involved in its production needs to be considered. Another consideration is the need for policy or legislation to monitor compliance through quality control measures, which may have an impact on the safety and effectiveness of the intended fortification effort. A key aspect of fortification is the need for partnerships and collaborations between the public and private sectors; they are essential to maintaining the success of fortification over time.

Supplementation programs

A successful example of a folic acid supplementation strategy is the NTD prevention program implemented in China following their effective community intervention trial. The supplementation strategy followed the approach taken in their intervention trial and targeted couples intending to get married at the time of a premarital health examination visit that was required for all couples in China at the time of the trial. At that visit, couples were offered an education session on the benefits of folic acid to prevent serious birth defects [6]. The program continued after the completion of the trial in 1996 and showed a continuing impact on the reduction of NTD to less than 5 per 10,000 pregnancies > 20 weeks of gestation until October 2003, when the regulation for premarital examination was rescinded.
and the examination was offered only on a voluntary basis [7]. As a result, in 2004 less than 5% of couples received the premartial examination and intervention, which led to a rise in the prevalence of NTD in 2004 to over 15 per 10,000 pregnancies > 20 weeks of gestation, a prevalence in the range of that found during the pre-supplementation period. That experience emphasizes that a successful supplementation program aimed at couples intending to have a pregnancy requires an active approach to contact the target group in order to deliver an effective educational intervention [7].

The success of the supplementation strategy in China emphasizes the crucial importance of reaching women before or at the time they contemplate a pregnancy. A supplementation strategy, such as the one implemented in China, can be an effective approach in countries or areas with a high frequency of intended pregnancies. Two essential elements of that strategy include a simple and feasible approach to identify couples contemplating a pregnancy and a successful educational component that will ensure consumption of optimal levels of folic acid before conception and through early pregnancy.

In countries where the rate of unintended pregnancies is high (> 50%), educational and social marketing approaches have targeted the general population as a way to reach all women of reproductive age. Educational and social marketing approaches have been studied in the Philippines, Cambodia, and Vietnam to test the efficacy of a program to promote daily and weekly supplements that contain iron and folic acid. Those studies found that, following a broad and intense social marketing campaign, women of reproductive age in the three countries were willing and able to purchase supplements if they were widely available and affordable. That was true among women of reproductive age in the three socioeconomic levels studied [8].

Mass education campaigns have been used in several countries to increase knowledge about the benefits of folic acid and promote consumption of supplements containing folic acid among a targeted group, with mixed success. The messages about folic acid, although directed to a target group, are delivered directly to the general public. Evaluations of mass media campaigns show that they can be an effective tool in increasing knowledge about folic acid, but their impact in increasing consumption of folic acid supplements appears to be limited. In the United States, mass education campaigns have had a positive effect in increasing knowledge about folic acid among women of reproductive age, but there has been little measurable effect in the intake of folic acid supplements [9, 10]. Telephone surveys conducted annually since 1995 have registered an increased awareness about folic acid (the respondents had heard or knew about folic acid), from about 40% to 84% in 2005. However, the percentage of women reporting regular intake of folic acid supplements has not changed significantly over a 10-year period, remaining at approximately 30% [9, 10].

In 1995, the Netherlands launched a mass media campaign to educate women of reproductive age about the importance of taking supplements containing folic acid before conception [11]. The campaign also targeted women of reproductive age through general practitioners, gynecologists, and midwife offices by placing posters with a folic acid message in their waiting rooms. Additionally, some areas with a high density of women of low socioeconomic status were targeted with further messages through alternative channels, such as free newspapers. Surveys of knowledge, attitudes, and consumption of folic acid were conducted in 1995, prior to the campaign, and again in 1996, about a year later. Knowledge about folic acid based on the percentage of women reporting hearing about folic acid before their last menstrual period rose from 42% in 1995 to 77% in 1996, but there were significant differences by socioeconomic level. Among women of low socioeconomic level, 28% reported knowing about folic acid before and 64% after the campaign. In the high socioeconomic level, 58% reported knowing about folic acid before, compared with 88% after the campaign. Those figures show a significant disparity in knowledge about folic acid among women in the low and high socioeconomic levels, even before the campaign. Similarly, there was an increase in folic acid use from 17% in 1995 to 49% in 1996, but with a large difference in folic acid use by socioeconomic level. Among women in the high socioeconomic level, 27% already consumed folic acid prior to the campaign; this rose to 62% in 1996. For those in the low socioeconomic level, only 10% were consuming folic acid in 1995; this rose to 39% in 1996. Although both groups increased folic acid use, nearly 60% of women in the low socioeconomic level were not consuming folic acid a year after the campaign began, indicating less concurrence between changes in knowledge and behaviors for women in lower than in higher socioeconomic levels [11]. Nonetheless, recent evaluation of the effect of the campaign on the prevalence of NTD in the Netherlands registered a 33% reduction, from 9.8 per 10,000 births in the years 1996–1999 to 6.5 in the years 2000–2002 [12].

In the United States, several strategies to educate women 18 to 39 years of age about the benefits of folic acid have been tested in a managed care group [13]. They have included direct mail messages and training of physicians to educate their patients about folic acid. The mail intervention consisted of a direct mail package that included a starter kit of 100 multivitamins and several keepsakes that had reminder messages about taking folic acid every day. The provider education intervention relied on primary care providers to deliver the message to women of reproductive age. Following a brief training by a nurse, providers were asked to include routine questions about folic acid use in all visits of women 18 to 39 years of age. The direct
mail intervention led to a 38% increase in consumption of multivitamins. However, this was not sustained after the intervention ceased, a fact that points to the importance of sustaining educational efforts [13]. The physician intervention did not show any increase in multivitamin consumption [13]. A survey of providers following the intervention showed very limited compliance in their role to mention or recommend multivitamins that contain folic acid during health visits of women in the target group.

Another important study addressed the traditional approach in public health of disseminating guidelines or advisories on specific issues that affect the health of the population. In an international review on the effect of recommendations or guidelines in reducing the prevalence of NTD, Botto and colleagues [14] found that the dissemination of public advisories on folic acid alone did not have an effect on the prevalence of NTD. That study reaffirmed the need to sustain specific, local, and effective interventions in order to maintain adequate consumption of folic acid over time and to reduce the prevalence of NTD.

Fortification programs

The success of folic acid fortification has been demonstrated in the United States, Canada, Chile, Costa Rica, and other countries. In the United States and Canada, fortification is directed at enriching cereal grain flour, while in other countries, vehicles such as milk and rice have been fortified. Most fortification regulations throughout the world are directed at mandating that specific products contain certain fortificants, but in the United States fortification with folic acid was accomplished by a redefinition of the standards of identity for enriched cereals. Therefore, the fortification mandate in the United States is only for cereal grain flours that carry an “enriched” label [15]. As a result, most of the corn flour consumed in the United States is not fortified because it does not carry an “enriched” label. In other countries, the regulation specifies fortification of specific cereal grain flours regardless of the use of an “enriched” label.

The folic acid fortification level was set at 140 µg/100 g cereal grain flour in the United States and at 150 µg/100 g in Canada [15, 16]. These levels were considered to represent an acceptable balance of benefit and potential risk and were estimated to deliver an average daily consumption of about 100 µg of folic acid [17]. An assessment after fortification in the United States suggested that the intake of folic acid from fortified food might be higher, possibly as a result of higher than expected fortified levels in foods [18]. However, it should be noted that while a greater than expected fortification level was found during the first year after mandatory fortification went into effect, more recent analyses indicate that the fortification level has declined substantially [19, 20].

In Chile, fortification is targeted solely at wheat flour because bread is universally and consistently consumed by women of reproductive age [21]. The fortification level was set at 220 µg/100 g, which was expected to deliver an average folic acid intake of 400 µg/day [21]. Costa Rica developed a fortification program that added folic acid to wheat flour, corn flour, milk, and rice in a staggered fashion. The first stage began with wheat flour fortified at 180 µg/100 g, followed by corn flour at the same level, and 1 year later milk was fortified at 0.4 mg/kg. Based on dietary surveys, the combination of fortified wheat and corn flour as well as milk delivered 232 µg/day, and with the recent fortification of rice, the average daily level should increase to 437 µg/day [22].

The effect of folic acid fortification in populations has been measured in terms of increased consumption of folic acid, changes in population-based serum and red blood cell folate levels before and after fortification, and reductions in the prevalence of NTD after fortification. Several countries have reported on these measures in the evaluation of their fortification programs. In Chile, a study comparing mean serum and red blood cell folate concentrations among women of reproductive age before and after fortification showed that serum folate rose from 9.7 nmol/L to 37.2 nmol/L and red blood cell folate rose from 290 nmol/L to 707 nmol/L [22]. In Costa Rica, Chen and Rivera [23] measured serum folate levels in a population of non-lactating women 15 to 44 years of age in metropolitan and rural areas of the country. Serum folate levels rose from 10.1 to 15.8 ng/mL in the metropolitan areas and from 9.6 to 12.5 ng/mL in the rural areas. In the metropolitan areas, folate deficiency declined from 19% prefortification to 2.5% postfortification. Similarly, in the rural areas, folate deficiency declined from 31.4% to 11.6% during the same periods [23]. In Canada, a study measuring red blood cell folate and serum B12 levels before and after fortification among women 18 to 42 years of age found that the mean red blood cell folate rose from 527 nmol/L prefortification to 741 nmol/L postfortification [24]. In the United States, the National Health and Nutrition and Examination Survey (NHANES) measured levels of serum and red blood cell folate before and after fortification [25]. Serum folate levels rose from a geometric mean of 12.0 nmol/L in the period 1988–1994 (prefortification) to 29.7 nmol/L in the period 1999–2000 (postfortification). Similarly, red blood cell folate rose from 398 to 636 nmol/L during the same two periods. Of note is that 16% of the population had low serum folate (< 6.8 nmol/L) in the prefortification period, compared with 0.5% postfortification.

Fortification with folic acid has had a major impact in reducing the prevalence of NTD in all countries...
where it has been implemented. In the United States, surveillance data in areas where prenatal diagnoses are taken into consideration have indicated that NTD prevalence in those areas decreased from 6.4 per 10,000 pregnancies pretreatment to 4.1 per 10,000 pregnancies post-treatment for spina bifida, and from 4.2 to 3.5 per 10,000 pregnancies for anencephaly [26]. The effect of fortification has been observed in all three major racial or ethnic groups in the United States, with postfortification spina bifida prevalence reaching 4.2 per 10,000 births among Hispanic women, 3.4 per 10,000 births among non-Hispanic white women, and 2.9 per 10,000 births among non-Hispanic black women, and postfortification anencephaly prevalence reaching 2.8, 2.0, and 1.8 per 10,000 births, respectively, for the three racial or ethnic groups [27]. In Canada, several studies reported significant decreases in the prevalence of NTD after fortification [28]. In Nova Scotia, the prevalence of NTD declined from 22.6 per 10,000 births to 11.7 in the 2 years following fortification [29]. Similarly, in Ontario, Quebec, and the provinces of Newfoundland and Labrador, NTD prevalences decreased by 48% to 5.8 per 10,000 pregnancies, by 32% to 12.8 per 10,000 births, and by 78% to 10.1 per 10,000 births, respectively, following fortification [30–32]. In Costa Rica, fortification began in 1998 and NTD prevalence declined from 97 per 10,000 births to 63 per 10,000 births after fortification [23]. In Chile, where fortification delivered on average 400 µg/day folic acid, the prevalence of NTD decreased from 17.1 per 10,000 births before fortification to 9.7 per 10,000 births, 2 years after fortification [33]. Thus, food fortification with folic acid has been a very successful saving approach for supplementation programs, but the investment may be beyond the capacity of some areas to implement.

Cost, benefits, and return on investment

In assessing the costs of a folic acid supplementation strategy, it is necessary to consider its essential elements, such as counseling or educational programs specifically designed to encourage women of childbearing age to consume folic acid supplements, as well as the cost of supplements and the needed monitoring and evaluation. Costs will vary depending on the intensity of the education and outreach, the level of the evaluation, and the size of the target group. Supplementation programs targeted at women of reproductive age might be less expensive than those directed at the general population. In countries where the frequency of intended pregnancies is high, such as China, efforts directed at women contemplating a pregnancy may also reduce the size of the target group and lower costs. In some settings, it might be possible to integrate outreach activities for NTD prevention with other public health outreach efforts that also target women of childbearing age, such as a preconceptional visit [34].

Supplementation programs tend to cost more than fortification on a per capita basis, in part because of the cost of supplements. In one estimate, the cost of a general educational campaign, without any outreach activity, was determined to be $0.04 per individual aged 15 years or older ( $10 million total) in the United States per year. However, the average annual cost of supplements was higher, approximately $11 per woman of childbearing age [35]. Studies from countries in the Western Pacific region showed that following education and social marketing, and with access to low-cost supplements, women of the reproductive age group, even those of low socioeconomic levels, will purchase and consume vitamin supplements [8]. Considering the results of one economic analysis, supplementation was found to be cost-effective if 15% of women of childbearing age not consuming folic acid supplements before the intervention would do so after the intervention [35]. This cost saving might be higher if the cost of supplements were lower, such as with the use of a weekly dose instead of a daily dose.

Weekly supplementation can be a practical and cost-saving approach for supplementation programs, but requires more community-based studies to ensure that serum and red blood cell folate levels can be attained within a similar range as daily supplementation. A study in New Zealand using 2,800 µg of folic acid once a week for 12 weeks found that red blood cell folate levels rose to an average of 900 nmol/L, but that level was lower than that found in the group receiving daily folic acid [36]. Among women receiving a weekly dose of folic acid, 49% reached a red blood cell folate level of ≥ 905 nmol/L, compared with 74% of women receiving folic acid daily. More studies are needed in different populations and geographic areas to address this question.

The cost of fortification includes the purchase of the premix that contains folic acid, the purchase and operation of the equipment needed in the milling process, the training of workers involved in the process, the cost of monitoring and quality assurance of the fortification process, and the public health evaluation of the health impact of the fortification program. In countries where fortification with other micronutrients is already implemented, the availability of the infrastructure will lower implementation costs. In Chile, the presence of other ongoing flour-fortification programs facilitated the subsequent inclusion of folic acid for the prevention of NTD. The expenses for the
mill industry in fortifying flour with folic acid were estimated to be $280,000 annually for adding folic acid to a flour premix and for analytic testing needed to ensure the appropriate fortification level of the end product. This cost, when considering only women of childbearing age in Chile, was reported as $0.16 per woman per year [33]. A similar situation existed in the United States, where fortification with folic acid was essentially an expansion of a policy on the enrichment of cereal grain flour that had already been in place for many years [17]. In one economic analysis, the annual expenses of fortification in the United States included the cost of folic acid ($4 million at a level of 140 µg of folic acid/100 g cereal grain flour), analytic testing ($2.5 million), and labeling changes ($4.5 million). Overall, the cost was estimated to be $0.06 per person ≥ 15 years of age [35]. Because NTD surveillance activities had already been in place as part of a larger birth defects surveillance system in both Chile and the United States, data on NTD prevalence were available to evaluate the long-term effects of interventions without incurring substantial additional costs. In the United States, opportunities were also available to monitor the serum or erythrocyte folate status of the population using the infrastructures of existing population-based surveys [25, 37, 38].

While an examination of costs alone is useful, a key public health question is the cost-benefit, or the return on investment. Before the policy on mandatory fortification with folic acid was adopted in the United States in 1996, several economic analyses were conducted to assess the potential economic impact in terms of NTD prevention [35, 39, 40]. The analyses varied in their assumptions and methodologies, but all demonstrated either a net benefit or a net cost saving. Based on these cost-benefit analyses, estimated benefits ranged from $100 million to $700 million per year at a folic acid fortification level of 140 µg/100 g enriched cereal grain flour, depending on whether potential costs of adverse effects such as masking of vitamin B_{12} deficiency were included [39, 40]. A separate cost-effectiveness analysis found that, compared with a reference of having no prevention program, each of several NTD prevention approaches (supplementation, fortification at 140 µg/100 g, 350 µg/100 g, or 700 µg/100 g enriched cereal grain flour) was associated with a cost saving in terms of years of life and quality-adjusted life-years [36].

More recently, another economic study was conducted [41] evaluating the impact of the mandatory fortification approach in the United States to prevent NTD (140 µg of folic acid/100 g enriched cereal grain flour), which has been in place since 1998. The study found an estimated observed net benefit ranging from $312 million to $422 million, and a cost saving ranging from $88 million to $142 million, both of which were greater than those projected before mandatory fortification was implemented. These effects were attributed to fortification, because the frequency of consumption of folic acid supplements among women of childbearing age in the United States remained essentially unchanged over the same period of time [41].

**Summary**

Intervention strategies to increase the consumption of folic acid have been shown to reduce folate deficiency in the target population, increase levels of serum and red blood cell folate, and reduce the prevalence of NTD. In countries with infant mortality rates below 30 per 1,000 live births, a reduction of NTD can lead to an important reduction in infant mortality [23]. The challenge for public health officials is to determine what interventions are best suited to reach optimal consumption of folic acid and other micronutrients in their areas. Promoting healthy dietary habits, such as dietary diversification, is the basis of healthy nutrition, and should be the starting point for any programs intending to prevent micronutrient deficiencies. However, to achieve adequate folate consumption for NTD prevention purposes, dietary diversification alone might not be sufficient. Supplementation and fortification are two approaches that have shown a positive health impact in reducing folate insufficiency, and have lowered the prevalence of NTD in different populations throughout the world.

A supplementation program to increase folic acid consumption based on educating couples prior to marriage in China, where pregnancy intendedness is high at the time of marriage, was shown to lead to optimal consumption of supplements containing folic acid and a significant reduction of NTD. Supplementation programs based on mass community education are promising but may not be as effective as targeted education. Mass communication interventions have shown an increase in knowledge of the population about folic acid, but their effect in increasing consumption of supplements has been mixed. Maintaining the success of supplementation programs over time requires a strong and persistent educational component and access to the supplements, which can add a significant cost to the intervention.

Fortification with folic acid has been shown to be an effective, sustainable, and cost-effective intervention to reduce folate insufficiency and reduce the prevalence of NTD in the countries where it has been implemented, such as the United States, Canada, Chile, and Costa Rica. The main challenges to fortification include identifying the appropriate vehicles, setting the optimal fortification level, sustaining quality assurance of the fortification level, and addressing regulations and trade barriers faced by some commercially fortified flours.

Supplementation and fortification are cost-effective and viable approaches to reduce the burden of NTD,
anemia, and other conditions resulting from folate deficiency. We believe that, eventually, evidence will emerge showing the feasibility of supplementation and fortification with vitamin B_{12}; and the practical experience with folic acid interventions will become useful for developing interventions involving vitamin B_{12}, should such interventions be determined necessary to reduce the effect of the vitamin deficiency.

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