Pros and Cons of Increasing Folic Acid and Vitamin $B_{12}$ Intake by Fortification

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There is no doubt that folic acid fortification can be effective for reducing the incidence of neural tube defects (NTDs). Flour is now fortified with this vitamin in more than 50 countries. Reductions in NTD have been substantial, amounting to 50% in populations with a high baseline prevalence of NTD and poor folate status. Other benefits of fortification have included a reduction in other birth defects and in prevalence of high plasma homocysteine, and possibly of mortality from stroke. However, since the onset of folic acid fortification, either mandatory or on the initiative of the food industry, questions have been raised about the possible adverse effects of this practice on the incidence of colorectal cancer and on immune function. These questions were raised because of significant associations between the adverse outcomes and folate status, unmetabolized folic acid in the circulation, or the timing of the initiation of fortification programs. They remain unproven. Some analyses also suggest that folic acid fortification can exacerbate the adverse effects of vitamin $B_{12}$ deficiency. For example, in national surveys in the United States, individuals with high serum folate concentrations (defined as $> 33$ or $> 59$ nmol/l in different studies) and vitamin $B_{12}$ deficiency (serum $B_{12} < 148$ pmol/l or methylmalonic acid $> 210$ µmol/l) had a greatly increased risk of cognitive impairment and anemia compared to those with $B_{12}$ deficiency and normal serum folate, and especially compared to those with normal status of both vitamins. Several studies also reported that when vitamin $B_{12}$ deficiency is accompanied by high serum folate, biomarkers of vitamin $B_{12}$ status become even more abnormal.

Most analyses of these questions have been conducted in wealthier countries based on data from elderly populations which have the highest prevalence of vitamin $B_{12}$ deficiency in these locations. However, of potentially greater concern is the increasingly common practice of folic acid fortification of flour in developing countries, where
folate status is probably often adequate even prior to fortification, and vitamin B₁₂ depletion or deficiency is common due to a low intake of animal source foods. It is clear that the percent reduction in NTD will be less where there is a lower incidence of NTD at baseline and folate status is initially better. It has been estimated that serum folate needs to be 16 nmol/l for maximum prevention of NTDs, and that this can be achieved with a daily folate intake of 474 dietary folate equivalents, or a folic acid intake of 279 µg/day, assuming no other dietary intake. It is likely that vitamin B₁₂ fortification would benefit many populations with a low intake of the vitamin; the prevalence of deficiency ranges from 5 to 30% in most countries and is 50% in India, and the prevalence of depletion is probably at least as high as that of deficiency. Vitamin B₁₂ deficiency is also strongly associated with risk of NTD, as well as low breast milk concentrations of the vitamin and delayed child development, cognitive impairment, depression, high plasma homocysteine, and possibly accelerated bone loss with aging. Thus, it would be rational to include vitamin B₁₂ as a fortificant along with folic acid. The Flour Fortification Initiative recommends fortification with 2 µg vitamin B₁₂/100 g of flour, a level which should improve status of the many elderly who cannot absorb the vitamin adequately from food, and of populations with a low intake of animal source foods. However, fortification trials using both vitamins have not yet been conducted.