Are we ready for mandatory fortification with vitamin B-12?1,2

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Fortification of food with micronutrients has played an important role in reducing common nutrient deficiencies worldwide, including the use of iodide to prevent goiter, vitamin D to prevent rickets, thiamine to prevent beri-beri, niacin to prevent pellagra, and iron to prevent anemia. These fortification policies have been great successes for public health. Today, when most of the population in developed countries is well-nourished, the authorities face different problems when they consider fortification policies.

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In the United States, Canada, and >50 other countries to reduce the incidence of neural tube defects (NTDs)—a relatively rare condition with an incidence of ∼1 per 1000 pregnancies, but with large regional differences. However, in Europe, there has been skepticism toward folic acid fortification, and, recently, the UK authorities delayed a final decision in order to further evaluate certain concerns and overall risks in specific groups in the population. So what are the concerns? According to some, there are none (1). However, studies based on large cohorts or trial evidence suggest otherwise (2). The most recent results suggest a potential increase in the risk of colorectal cancer (3, 4), but, from the very beginning, there has been concern about the possible masking of vitamin B-12 deficiency. Masking of vitamin B-12 deficiency, ie, prevention of anemia but not of the neurological consequences, may occur when unmetabolized folic acid reaches the circulation; this has been shown experimentally as well as clinically (5). Folic acid is likely to appear in the blood at doses >400 μg/d (5) and to appear in substantial concentrations when total serum folate concentrations exceed 50 nmol/L (6). After folic acid fortification in the United States, ∼25% of the elderly and of children aged <11 y have folate concentrations >50 nmol/L (7).

Recent data from the US National Health and Nutrition Examination Survey (NHANES) indicate that the function of vitamin B-12 deteriorates as serum folate status increases in persons who are deficient in vitamin B-12 (8). More seriously, the data show that persons with both low vitamin B-12 and high folate concentrations were at particularly high risk of memory impairment and anemia (9). In the NHANES cohort, the proportion of elderly with a high folate and low vitamin B-12 status was 4% (9). If the same proportion of all elderly in the United States is affected, then some 1.8 million US elderly might be at increased risk of cognitive impairment and anemia because of an imbalance between folate and vitamin B-12 (10). Other studies also hint at the importance of maintaining a good balance between vitamin B-12 and folate status for cognition (11), for prevention of breast cancer (12), and possibly for the prevention of diabetes in the offspring (13).

In this issue of the Journal, Winkels et al (14) ask a timely question, ie, will bread cofortified with folic acid and low-dose vitamin B-12 improve vitamin B-12 status in a relevant target population? This question has been investigated before and perhaps is best documented by Tucker et al (15). Both studies showed that, in a relatively healthy group of middle-aged to elderly persons, consumption of bread or cereal fortified with low-dose vitamin B-12 improves vitamin status, as determined by blood vitamin concentrations and functional markers such as total homocysteine, homocysteine, vitamin B-12, and methylmalonic acid. Thus, by adding small amounts of vitamin B-12 to grain, it is possible to improve vitamin B-12 status in a large part of the population.

So, why not introduce vitamin B-12 fortification now? It might help to avoid the potential problem of masking vitamin B-12 deficiency as well as memory problems and anemia in those with an imbalance between low vitamin B-12 and high folate. Irrespective of folic acid fortification, it may also be good for those sections of the populations that are known to have compromised vitamin B-12 status, such as vegetarians, breastfed infants, and, in particular, the elderly, up to 15% of whom suffer from food-cobalamin malabsorption. Fortification with vitamin B-12 will probably not, however, have any impact on the 2–3% of elderly who have pernicious anemia, but it might prevent NTDs that are suspected to be due to poor cobalamin status (16).

According to the Institute of Medicine, no adverse effects have been associated with excess vitamin B-12 intake from food or supplements in healthy individuals. One possible reason for the low toxicity risk may be that only a small proportion of vitamin B-12 is absorbed from the gastrointestinal tract. Furthermore, in contrast with folate, which is a substrate, vitamin B-12 only acts as a cofactor. Thus, on the face of it, one may argue that mandatory vitamin B-12 fortification should be introduced without

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delay (17, 18), particularly in countries that already have folic acid fortification. Nevertheless, before this step is taken, it is essential that government authorities ensure that the required investigations are performed and provide the funding for them (19), and thereby give assurance that vitamin B-12 fortification will be safe as well as effective. Some of these investigations include the following:

1) dose-response studies in persons with low vitamin B-12 status due to food-cobalamin malabsorption, the most common cause of low cobalamin status in elderly.
2) evidence of benefit from randomized trials using low-dose vitamin B-12 with clinical outcomes; current trial evidence even from high-dose trials is far from unequivocal (20).
3) evidence of a lack of adverse effects in large-scale trials; thus far, studies have not been designed to assess such effects. We should not ignore observational studies that have reported an association of B-12 status (21) or intake (22) with an increased risk of cancer.
4) stability studies: the most commonly used supplement, cyanocobalamin, is rather unstable and may form cobalamin analogues that interfere with normal cobalamin metabolism and transport (23, 24).
5) before fortification is introduced, a coherent plan should be developed to document changes in vitamin B-12 status; to monitor the effects on NTD births, on cognition, and anemia in the elderly; and to assess the possible occurrence of untoward effects on the population.
6) while waiting for a decision on vitamin B-12 fortification, authorities urgently need to consider how to manage the newly discovered large-scale problem of those with low vitamin B-12 status and high folate status in countries who have fortified with folic acid (10).

In relation to folic acid fortification, it was recognized that NTDs were rare but, at the time, those in favor focused on the huge “potential” additional benefits that fortification might have, particularly in relation to cardiovascular disease. Others were called unethical for raising concerns and for wanting to wait for trial evidence in relation to cardiovascular disease. Furthermore, folic acid was considered safe, without further trial evidence. The situation is rather different for vitamin B-12 fortification, where the scale of the problem is potentially much greater, including not only a significant proportion of the elderly but also some infants and young children with low vitamin B-12 status. Furthermore, there is perhaps less concern about adverse effects with this vitamin than there was with folic acid. However, we must remember that evidence of benefit and of lack of harm is always needed before introducing mandatory population-level exposures to nutrients (19).

The authors are on the management committee of an ongoing trial of B vitamins (including vitamin B-12) in the elderly (ISRCTN94410159).

REFERENCES