Reviewer's report

**Title:** Effectiveness of the National Program of Complementary Feeding for older adults in Chile on vitamin B12 status in older adults; secondary outcome analysis from the CENEX Study (ISRCTN48153354)

**Version:** 1  **Date:** 30 January 2013

**Reviewer:** G P Oakley Jr.

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I agree with your main conclusion that the current B12 supplement program for older people does not work to improve serum B12. I think this is likely because not enough of the fortified foods were eaten and perhaps that the dose of B12 was too low. Also, there is ample published literature that older people who consume 6 or 25 micrograms of B12 in multivitamins have much better serum B12 concentrations and I suspect, but don't know if any literature that has looked 1.5 micrograms a day. I would expect it to be effective so I would think some how the subjects just did not eat the product.

I think you miss a great opportunity to say that if flour fortified if B12 to have the average person consume say 10 micrograms of B12 a day that B12 deficiency among older people would be reduced by 70% and that the average B12 concentrations would increase. I suggest you have this a major point of the discussion and conclusion.

Why would I say this? Your serum folate data show that there was no folate deficiency and probably no folate deficiency anemia in your subjects. This is a remarkable and predictable and desirable result from required fortification of flour. It has been well reported from several studies that people who take multivitamins with 6 to 25 micrograms of B12 in them have a remarkable increase in their serum B12 in groups and that the proportion of those with B12 deficiency no matter how defined, is reduced by about 70%. You had no reduction in B12 deficiency or increases in your serum B12 concentrations. If you had a before and after with B12 fortification of flour to add a median of 10 micrograms a day--most would get at least 6 then, the existing data would predict a remarkable--70% reduction in B12 deficiency and a remarkable increase in serum B12 concentration among older people. I suggest that the other main conclusion for this paper is that 70% of the B12 deficiency in older people in Peru could be solved by requiring B12 fortification. May I suggest a look at RJ Berry work from CDC on NHANES data. It a remarkable set of papers. The JAMA research letter: Vol 300, pages 2486 to 87 1998 was the first one and shows in the figure that the median serum folate in each of the quintiles is similar for people who get folic acid only from mandatory flour fortification and the state in the text that this group of people in each quintile consume about 140 micrograms of synthetic folic acid as a result of consuming products with mandated fortification. I think these data make it reasonable to conclude that flour
fortification in the USA and Chile is a remarkably good way to assure that the population gets a constant amount of B vitamins added to the flour.

Of course the B12 deficiency that is most important is the among those in the 30% who cannot maintain a normal serum B12 after consuming 6 to 25 micrograms of B12. It is likely that they have an absorption problem such as early and undiagnosed pernicious anemia that requires lifelong treatment with much higher--500 to 1000 micrograms oral or injection doses of B12. If the flour were fortified with B12 there would be fewer people with deficiency and the ones remaining would need medical evaluation. These people need it now, but they are mixed in with more than twice as many people with low serum b12 that is cured or prevented with 6 micrograms.

Another important point in the tables is the low level of anemia and macrocytosis--no doubt a success of the folic acid fortification of flour--a not widely discussed benefit of folic acid fortification.

A less important, but still important issue is the paragraph beginning on the bottom of page 8 with "Considering that hematological disorders as anemia and macrocytosis... is a very poor paragraph and not supported by evidence. My problems with it:

1. Hematological indicators of PA have always been poor ones as people can have serious neurological disease with no hematological indicators. This continues. If a patient has such symptoms, they need to be worked up, of course, but not a very sensitive way to find people with PA.

2. It is simply not true that folic acid fortification tends to mask high prevalence of B12 deficiency in older adults and your data clearly show this. You have very good serum folate concentrations with no folate deficiency yet you have continuing B12 deficiency. Although very high doses of folic acid 5 to 50 milligrams can some time cure the anemia of B12 deficiency, the evidence does not suggest that the 140 micrograms or even 400 micrograms that would occur after fortification can cure the anemia of B12 deficiency. This idea of "masking" is a poor idea, not data driven and I think time not to include in papers as it is confusing and likely simply wrong way to thing. I prefer to think that there are people with B12 deficiency, it is independent of folate issues and needs to be addressed as a B12 issue not a folate issue. The sooner we all focus on the real problem--B12 deficiency--the sooner we will improve the lives of people with B12 deficiency. Your paper points out clearly there is work to be done to solve the B12 deficiency. In my view that is simply to get enough B12 to our older population, starting with fortification of flour with B12.

The paper needs another read by authors to make sure English is tighter.