Assessing the case for mandatory folate fortification: policy-making in the face of scientific uncertainties

Abstract

This paper presents the view that policy-makers face scientific uncertainties in assessing the case for mandatory folate fortification as a policy response to epidemiological evidence of the relationship between folate and neural tube defects. Moreover, the resolution of these uncertainties is confounded by the under-resourced state of nutrition information systems in Australia and New Zealand. The uncertainties relate to potential risks and benefits associated with the intervention for the target group and the population in general. These risks and benefits reflect the mismatch between evidence and policy that arises when addressing a presumed genetic abnormality in at-risk individuals with an intervention that is population-wide in its scope. There is an urgent need to conduct ongoing national nutrition surveys and monitor and evaluate policy interventions to strengthen the capacity of nutrition information systems to inform decision-making for this current, and future, public health nutrition policy.

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The policy-making process for public health nutrition strives to be evidence based. Food Standards Australia New Zealand[1] is assessing the case for mandatory folate fortification of certain foods as a policy response to epidemiological evidence that the risk of a neural tube defect (NTD)-affected pregnancy is inversely associated with folate status during the periconceptional period.[2] However, scientific uncertainties dominate the policy-making process. With the same evidence available, policy outcomes differ among countries and debates are occurring among scientists.

Uncertainties in the epidemiological evidence

Epidemiological studies are unable to reveal the biological mechanism by which folate reduces the risk of NTDs. It is known that folate's protective effect is conferred optimally when it is consumed in pharmacological 'doses', i.e. amounts several times the recommended dietary intake, compensating for impaired folate metabolism in susceptible individuals rather than correcting a frank nutritional deficiency as such. In this context, folate is acting more as a therapeutic agent than as a conventional nutrient. The findings illustrate why folate is at the forefront of 'nutrigenomics', the sub-discipline within human nutrition involved in the investigation of the interaction between nutrition and gene function.[3] From this perspective, promoting folic acid supplement use by at-risk individuals during the periconceptional period would be a logical policy response to the epidemiological evidence.

However, the effective promotion of folic acid supplement use to at-risk individuals is confounded by several peculiar circumstances. First, knowledge about specific genotype associations is incomplete and it is not possible to screen for women at risk of having an NTD-affected pregnancy. Second, the closure of the neural tube occurs by the 28th day after conception, a time when a woman may be unaware that she is pregnant and may not realise the importance of increasing her folate consumption. Third, in Australia and New Zealand it is estimated that almost half of pregnancies are unplanned. Therefore, all women of child-bearing age are the target group for a public health strategy. Mandatory folate fortification improves the likelihood that the target group will be exposed passively to increased amounts of folic acid.

The peculiar circumstances associated with translating the scientific evidence of the folate-NTD relationship into a policy response present a dilemma for policy-makers. Neural tube defects are diseases of particular severity and contribute considerable emotional, economic and social cost to families with affected pregnancies. However, NTD prevalence is low, with up to 500 pregnancies in Australia[4] and 30 live and still births in New Zealand[5] affected each year. If mandatory folate fortification were to proceed it would represent a mismatch between the nature of the health problem and the scope of the policy response. For these reasons mandatory folate fortification has

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been described as a population-wide "uncontrolled clinical trial".[6] This mismatch raises questions about the potential risks and benefits of mandatory folate fortification not just for the target group, but for the population as a whole.

Uncertainties in the evaluative evidence of risks and benefits

Mandatory folate fortification has not been implemented and would create a food fortification policy precedent in Australia and New Zealand; thus, risks and benefits associated with this policy cannot be predicted with certainty. Within the constraints of this paper, the main risks and benefits described in current policy documents[1,5] and evaluative evidence from population-based interventions and trials are discussed briefly. As research of folate and health relationships continues and more evidence emerges, understanding of risks and benefits may change.

Risks

The primary potential concern noted for the target group from elevated folate status is the trend towards increased risk of multiple gestation associated with folic acid supplementation as described in the relevant Cochrane review[2] and more recently in an observational study from Sweden.[7] Uncertainties cloud the interpretation of the available evidence. For example, questions have been raised regarding whether analyses have adequately adjusted for possible confounders.[8] Also, an increased prevalence of twinning was not found in a large intervention study in China,[9] or in the United States (US), where mandatory folate fortification of cereal grains was introduced in 1996.

The long-term consequences of exposing population groups to novel levels of synthetic folic acid derived from folate-fortified foods cannot be predicted accurately. The experience of the unexpected, and harmful, outcomes from trials of beta-carotene supplements[10] highlights the difficulty in anticipating outcomes from manipulating exposure to nutrients. Elevated folate status may interfere with the action of certain drugs, including anticonvulsants and folate antagonists.[6] More broadly, high doses of folate have been reported to be associated with the masking of clinical symptoms of vitamin B_{12} deficiency.[6] The key features of vitamin B_{12} deficiency are macrocytic megaloblastic anaemia and neuropathy. Unless adequate vitamin B_{12} is administered, the underlying neuropathy persists, leading to irreversible neurological damage. The postulated increased risk of masking anaemia has not been reported in the US since mandatory folate fortification was introduced. Some have asked whether the necessary studies to assess adverse outcomes have been undertaken in the US.[11]

Benefits

In the US and in Nova Scotia, Canada, the prevalence of NTDs has decreased by 27%[12] and more than 50%,[13] respectively, since the introduction of mandatory folate fortification of cereal grains. There are several uncertainties in determining the contribution of mandatory folate fortification to these outcomes. First, declining rates in the birth prevalence of NTDs have been observed in many countries over several decades, although increases in prenatal NTD diagnosis and terminations are believed to be significant explanatory factors of such trends. Second, alternative policy interventions have been implemented in the US and Canada since the late 1990s, e.g. promotion of folic acid supplement usage. Third, findings from population-based studies in China[14] and Canada[15] indicate that NTD prevalence reduction is associated with baseline NTD and obesity prevalence, respectively.

A population health benefit from mandatory folate fortification would be demonstrated by evidence either of a correction of existing folate deficiency among the population or that elevated folate status helps prevent chronic disease. There is a lack of evidence of population-wide folate deficiency in Australia and New Zealand. Conversely, there is much speculation about potential 'functional' roles for elevated folate status, particularly those roles mediated via the lowering of the mean blood concentrations of homocysteine in the population and a subsequent reduction in the incidence of cardiovascular disease. However, it is uncertain whether homocysteine levels are a causative agent of cardiovascular disease and the observational studies that have provided evidence of an association are unable to demonstrate conclusively that increasing folic acid intake will reduce cardiovascular disease risk.

Uncertainties associated with nutrition information systems

The uncertainties in the evaluative evidence associated with the potential risks and benefits highlight the importance of nutrition information systems to support policy-making. Yet governments in Australia and New Zealand have not invested substantially in the development of nutrition information systems. Indeed, generally governments have done very little to support the implementation of non-mandatory folate fortification policy options. Therefore, there has been a lack of opportunity to collect data to undertake a risk-benefit analysis of the relative effectiveness of policy alternatives to reduce the risk of NTDs.

When alternative policy interventions have been implemented there has been a lack of monitoring and evaluation. In 1994, the NHMRC's Expert Panel on Folate Fortification stated that monitoring would be undertaken to enable the reporting of progress against voluntary folate fortification policy targets within three years.[16] Yet, in 2000, in its interim report on voluntary folate fortification, the Australian Food and Nutrition Monitoring Unit commented that no monitoring of the folate levels of folate-fortified foods had been undertaken and there were serious gaps in Australia's capacity to monitor changes in rates of NTDs. The unit concluded that, "In Australia, it is too early to assess the impact of folate fortification on the occurrence of NTDs, and mechanisms are not in place to monitor other health outcomes".[17]

Moreover, there is a lack of broader food and nutrition monitoring and surveillance activities. It is 10 and eight years since Australia and New Zealand, respectively, have conducted

comprehensive national nutrition surveys. Since the mid-1990s, dietary behaviours and food product availability appear to have changed dramatically. There is a lack of baseline data on the population's dietary nutrient intake and nutrient status to inform food fortification policy-making. It does not appear that this situation will change should mandatory folate fortification be introduced in Australia in the near future. On 10 February 2004, in response to a question taken on notice, the Minister for Health and Ageing replied: "No preliminary work or planning has been undertaken for conducting a follow-up National Nutrition Survey."[18]

The scientific uncertainties illustrate that despite the compelling evidence of the folate-NTD relationship, a definitive policy response may not necessarily be apparent. The uncertainties are exacerbated because policy-makers are expected to formulate decisions with a lack of information about the effectiveness of policy alternatives, the nutrient status and dietary intake of the population. They cannot have confidence that policy will be implemented as planned and sufficiently monitored and evaluated to ensure that it does more good than harm. There is an urgent need to conduct ongoing national nutrition surveys and monitor and evaluate policy interventions to strengthen the capacity of nutrition information systems to inform decision-making for this present, and future, public health nutrition policy.

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