BMA calls for mandatory folic acid fortification to reduce the risk of neural tube defects

A briefing from the BMA Board of Science – March 2013

This briefing paper sets out BMA policy on mandatory folic acid fortification as a way to reduce the risk of neural tube defects. It provides background information, highlights the evidence for the role of folic acid in neural tube development, and considers the key issues in implementing mandatory fortification.

BMA policy

At the BMA’s 2012 Annual Representative Meeting (ARM), members expressed concern about the number of pregnancies in the UK that are affected by neural tube defects (NTDs). We are calling on the UK governments to introduce legislation requiring the mandatory fortification of flour with folic acid. This is an important public health measure to reduce the risk of these common birth defects occurring.

Neural tube defects

Neural tube defects are severe birth anomalies that result from failure of the neural tube to close properly, approximately 28 days postconception. They are a leading cause of infant mortality worldwide, and are associated with a range of complications that can cause severe disability and morbidity.

Two of the most common NTDs are spina bifida and anencephaly. Anencephaly results from failure of fusion of the anterior (cranial) neural tube. Many children with anencephaly are stillborn or die shortly after birth. Fifty per cent have a life expectancy of between a few minutes and one day, and 25 per cent only live up to 10 days. On very rare occasions the infant can survive, with continuous life support and intensive care, for up to one month. Spina bifida results from failure of fusion of the posterior (caudal) neural tube. There are three principal types of spina bifida – occulta, meningocele and myelomeningocele – each with varying degrees of severity. Myelomeningocele is the most common and severe form. It is a defect in which the bones of the spine do not completely form, resulting in an incomplete spinal canal. Children with myelomeningocele have a high probability of lifelong physical and mental handicap, and only a minority of these children are able to function independently as adults. The majority of children with myelomeningocele will have associated hydrocephalus. This occurs when either too much cerebrospinal fluid (CSF) is produced or when it is stopped from circulating or being re-absorbed. The CSF builds up within the ventricles of the brain resulting in increased pressure on the brain.

Folate and neural tube defects

The term folate is used to describe a family of B-group vitamins that includes:
- naturally occurring folates found in some foods such as liver, yeast extract, and various green leafy vegetables
- folic acid which is the synthetic form used in supplements and added to fortified foods (e.g., breakfast cereals and some fat spreads).

Folate is essential for the synthesis of nucleic acids and amino acids, and is required by the body for cell division and cell maintenance. While the specific relationship between folate and the pathogenesis of NTDs is largely unknown, folate status has been found to be associated with the risk of NTDs in an inverse dose-response relationship. A 1995 study by Daly et al established that increasing levels of blood-circulating folate were associated with decreasing incidence of NTDs. The magnitude of the NTD reduction rate was relatively proportional to the initial level of blood folate.

Occurrence of neural tube defects

In the UK, the occurrence of NTDs has declined significantly in the last 30 years, with reported rates of approximately 3.2 per 1000 births in England and Wales in 1970. This can in part be attributed to the effect of improved antenatal screening, an increase in terminations after prenatal diagnosis of an NTD,
and the introduction of folate fortification of cereals in the 1970s. Despite these measures, the UK still has the highest levels of NTDs in Europe, with a prevalence rate ranging from 0.8 to 1.5 per 1000 births, depending on ethnic, geographic, and nutritional factors.

Reducing the risk of neural tube defects

There is a substantial evidence base demonstrating that increased folate intake can reduce the risk of NTDs occurring in pregnancy. A number of reviews have found that folic acid supplementation and fortification are effective public health strategies for reducing neonatal mortality from NTDs.

It is worth noting that not all NTDs can be prevented by increasing the intake of folic acid. The existence of a ‘floor effect’, independent of the amount of folic acid administered, has been found to occur in countries with mandatory fortification programmes. Data suggest that a prevalence of 0.5 to 0.6 cases per 1000 pregnancies represents the lowest prevalence that is achievable through folic acid fortification.

Folic acid in combination with multivitamin supplements has also been shown to reduce other congenital anomalies, including a broad range of heart defects (in particular ventricular septal defects and some conotruncal defects), urinary tract anomalies, oral facial clefts, limb defects, and pyloric stenosis.

Supplementation versus fortification

The critical period for ensuring adequate folate levels is during the first 28 days following conception (ie during the perinatal period before closure of the neural tube). Guidance from the UK health departments recommends ‘all women who could become pregnant should take 400µg [0.4mg] folic acid per day as a medicinal or food supplement prior to conception until the twelfth week of pregnancy’.

Encouraging women to consume a daily supplement has a number of limitations:

- it does not take account of unplanned pregnancies – this is particularly important as it is estimated that almost half of all pregnancies in the UK are unplanned. Under these circumstances, a woman may not know she is pregnant, and is unlikely therefore to take supplements during the critical early phase of embryonic development.
- there is poor compliance with the advice to take folic acid supplements preconceptually. A 2009 UK cohort study found that women planning a pregnancy only marginally increased their compliance with folic acid supplement use. The 2005 UK Infant Feeding survey found that 79 per cent of mothers in the UK reported that they knew why increasing folic acid in the early stages of pregnancy was recommended, and 83 per cent of all mothers reported taking some action to increase their folic acid intake. The survey, however, also noted that, although 75 per cent of women stated that they took folic acid supplements, they may have taken them only after realising they were pregnant. Educational campaigns encouraging women to increase their use of supplements have not been effective at reaching every high-risk population.

These limitations can be overcome by the implementation of a mandatory folic acid fortification programme. A 2006 report by the Scientific Advisory Committee on Nutrition (SACN) recommended mandatory folic acid fortification as the most effective way to increase folate intake of women most at risk of NTD-affected pregnancies, provided voluntary fortification is controlled and advice is given about supplement use. International experience has demonstrated that mandatory fortification programmes can be effective at reducing the rate of NTDs by between approximately 25 and 50 per cent (see Table 1).

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1 It is worth noting that mandatory folic acid fortification has not been introduced in any European countries, and there are no examples where mandatory folic acid fortification programmes have been introduced and subsequently stopped.
Table 1 – overview of mandatory folic acid fortification programmes internationally

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<thead>
<tr>
<th>Country</th>
<th>Type of fortification</th>
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<tr>
<td>United States</td>
<td>1998 – mandatory folic acid fortification of enriched breads, cereals, flours, corn meals, pastas, rice, and other grain products.</td>
<td>A study by the Centers for Disease Control and Prevention estimated that since the addition of folic acid in grain-based foods, the rate of NTDs dropped by 25 per cent in the United States.</td>
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<tr>
<td>Canada</td>
<td>1998 – mandatory fortification of enriched flour and uncooked cereal grains.</td>
<td>A seven-province study from 1993 to 2002 showed that the prevalence of NTDs in Canada decreased from 1.58 per 1000 births before fortification to 0.86 per 1000 births during the full-fortification period.</td>
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<tr>
<td>Chile</td>
<td>2000 – mandatory fortification of flour.</td>
<td>During the pre-fortification period (1999-2000) the NTD rate was 17.1 per 10,000 births in a total of 120,566 newborns. During the post-fortification period (2001-2009) the NTD rate decreased to 8.6 per 10,000 births in a total of 489,915 newborns, which translates into a rate reduction of 50 per cent for all NTDs.</td>
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Is folic acid fortification safe?

In the UK, a guidance level of 1mg per day of folic acid has been set for adults. A daily intake at or below this level has not been found to cause harm to the general population, and a daily dose of folic acid between 0.4 and 1.0mg is not known to cause harm to the developing fetus or the pregnant woman. There is no evidence of any adverse side effects associated with folic acid intake levels below 1mg per day. Extremely large dosages (more than 15 mg), however, can result in digestive problems, insomnia, skin reactions, and seizures. Provided there are appropriate controls on voluntary fortification / supplementation – to ensure that individuals do not exceed the upper intake level of 1mg per day – there is no evidence to suggest any adverse harm from the introduction of a mandatory folic acid fortification programme.

The risk of masking vitamin B12 deficiency in the over 65s has been cited as an objection for folic acid fortification. The 2006 SACN review concluded that masking of vitamin B12 deficiency is not associated with doses of folic acid up to 1mg per day. There are no reports from countries that have introduced mandatory fortification indicating deleterious effects on older people with low vitamin B12 status. Concern has also been expressed that mandatory fortification at oral doses of 0.26mg or greater may cause liver damage due the presence of unmetabolised folic acid in the blood. Available data are insufficient to adequately assess the long-term effects of exposure to unmetabolised folic acid, and the SACN did not find any evidence of adverse effects of unmetabolised folic acid. The SACN also concluded that the evidence for an association between folic acid and increased or reduced cancer risk in humans is equivocal.

In October 2007, the SACN was asked by the Chief Medical Officer (CMO) for England to consider two studies suggesting that folic acid may increase the risk of colorectal cancer. The SACN concluded that the new evidence does not provide a substantial basis to change its previous recommendation for the introduction of mandatory folic acid fortification.

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*UK guidance levels have not been set for children. Tolerable upper levels have been set for children in Europe and the USA based on body weight. In Europe, the following levels apply for children: 4-6 years, 300 µg per day; 7-10 years, 400 µg per day; 11-14 years, 600 µg per day; 15-17 years, 800 µg per day.*
**Government policy on mandatory folic acid fortification**

In October 2009, the Food Standards Agency (FSA) advised the CMO of the outcome of the SACN’s review. The CMO was expected to advise UK Health Ministers of the SACN’s recommendation thereafter, and Health Ministers in England, Scotland, Northern Ireland and Wales would then decide whether to approve mandatory folic acid fortification in the UK. The FSA are still awaiting direction from UK Health Ministers. If mandatory fortification is approved the FSA in Northern Ireland, Scotland and Wales, and the Department of Health in England, will consider how this should be implemented.

**Fortification of flour**

Flour is an appropriate vehicle for fortification as a large proportion of the UK population regularly consume flour-based products. Sixty per cent of flour produced in the UK is used in the manufacture of bread, and bread is purchased by 99 per cent of British households. The UK also currently requires the fortification of flour with calcium, thiamine, iron and niacin.

The use of flour-based products for mandatory folic acid fortification is supported by the Department of Health Committee on Medical Aspects of Food and Nutrition Policy, the SACN, and the FSA. In its 2006 review, the SACN concluded that between 47 and 378 NTD-affected pregnancies could be prevented, per year, by the fortification of flour with folic acid (see Table 2).

The introduction of mandatory fortification of flour with folic acid would need to be accompanied by advice for women of child bearing age who do not consume any flour-based products. This group may include those with coeliac disease, those with gluten sensitivity, some individuals with irritable bowel syndrome and those on gluten free or carbohydrate free diets.

<table>
<thead>
<tr>
<th>Level of folic acid fortification</th>
<th>Number of NTD-affected pregnancies prevented</th>
<th>Reduction in risk percentage</th>
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<tbody>
<tr>
<td>100g/100g flour</td>
<td>47-99</td>
<td>7-11%</td>
</tr>
<tr>
<td>200g/100g flour</td>
<td>91-198</td>
<td>13-22%</td>
</tr>
<tr>
<td>300g/100g flour</td>
<td>126-285</td>
<td>18-32%</td>
</tr>
<tr>
<td>450g/100g flour</td>
<td>175-378</td>
<td>25-42%</td>
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Source: Scientific Advisory Committee on Nutrition: Disease and Prevention. SACN. London: The Stationary Office

**Cost-effectiveness**

There are limited data on cost-effectiveness of folic acid fortification programmes. A 2012 review of contrasting strategies for the prevention of NTDs estimated that the annual cost saving of folic acid fortification in UK would be £5.1 million. These findings are supported by a 2011 literature review of international prevention programmes, which concluded that folic acid fortification in food is a cost-effective way to reduce the incidence and prevalence of NTDs.

**Ethical considerations**

A 2007 report – commissioned by the FSA and produced by the Institute for Science and Society at the University of Nottingham – examined the ethical implications of options for improving the folate intake of young women. The report concluded that available evidence suggests that widespread fortification of flour products will result in a lower incidence of NTDs cases in the population as a whole. It is likely that the greatest reduction would occur in lower socio-economic groups. It therefore fulfils the objectives of

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1 This figure was calculated based on estimates of the number of pregnancies affected by NTDs that could be prevented by folic acid fortification (273 per year) and the cost saving benefits associated with preventing these (£5.2 million), as well as the cost to the UK government of mandatory folic acid fortification (£728,000 per year).
social responsibility, benefit to individuals and society, protection of vulnerable young women, and reduction in health inequalities. The report identified the following common ethical difficulties inherent in population-wide health programmes:

- **mandatory fortification removes the personal choice of those affected** – if all flour-based products in the UK are fortified then there is a strong likelihood that many individuals will consume products fortified with folic acid without their prior informed consent.
- **mandatory fortification may breach the principle of non-stigmatisation** – active campaigns to eliminate NTDs cases may encourage the belief or impression that those individuals who suffer from NTDs are of less value than those who do not. It may also send the message that women whose children suffer from NTDs are somehow at fault because they did not follow recommended health guidelines during pregnancy.

In evaluating the ethical considerations, the report concluded that although mandatory fortification would come at some cost to individual autonomy, the opt-out procedures largely comply with the ethical requirements. Mandatory fortification would also ensure that there were no price distinctions to disadvantaged consumers. The report recommended that should mandatory fortification be adopted, the FSA should be careful to ensure that its decision cannot be represented as a devaluation of the personhood of those already born with NTDs, or as a criticism of the competence of their mothers.

This echoes the findings of the Nuffield Council on Bioethics 2007 report on public health and ethical issues. This noted that folic acid fortification is not known to be associated with harm and that the FSA’s proposal would exclude wholemeal flour / bread from the policy, enabling individuals to opt out of receiving fortified foods, thereby complying with ethical requirements. It is also in line with the Nuffield Council’s ‘ladder of interventions’, which sets out different levels of intervention in the interests of public health. The least intrusive step is to do nothing, and the most intrusive is to legislate in a way which restricts choice. The 2011 House of Lords Science and Technology Committee enquiry into behaviour change has drawn on the Council’s ‘ladder of interventions’ to conclude that a whole range of measures – including some regulatory measures – will be needed to change behaviour. This position is supported by the BMA’s 2012 paper *Behaviour change, public health and the role of the state – BMA Position Statement*.

**Conclusion**

Folic acid fortification of flour is a cost-effective public health strategy for reducing NTDs in a population. It has been found to be highly protective against NTDs and there is no evidence of any adverse risk to human health, provided there are adequate controls on voluntary fortification and supplement use. The BMA strongly supports the mandatory fortification of flour with folic acid as a public health measure to reduce the number of pregnancies affected by NTDs. This should be accompanied by advice for women of child bearing age who do not consume any flour-based products.
References


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