Folic acid intake before and during pregnancy reduces neural tube defects (NTD). Therefore, several countries have enriched bulk food with folic acid resulting in a 26–48% decrease in the prevalence of NTDs. In 2000, the Dutch Health Council advised against folic acid enrichment based on literature research; yet formal cost-effectiveness information was absent. We designed our study to estimate cost-effectiveness of folic acid food fortification in the Netherlands. Method: Prevalence of NTD at birth, life-time costs of care, and folic acid fortification costs were estimated using Dutch registrations, Dutch guidelines for costing, (inter)national literature and expert opinions. Both net cost per discounted life year gained and net cost per discounted quality adjusted life year (QALY) gained were estimated for the base case and sensitivity analyses. Results: In the base case and most sensitivity analyses, folic acid enrichment was estimated to be cost-saving. Bulk food fortification with folic acid remains cost-effective as long as enrichment costs do not exceed €5.5 million (threshold at €20,000 per QALY). Conclusion: Our model suggests that folic acid fortification of bulk food to prevent cases of NTD in newborns might be a cost-saving intervention in the Netherlands. Additionally, besides the evidence that folic acid reduces the number of NTDs, there are indications that folic acid is associated with the prevention of other birth defects, cardiovascular diseases and cancer. Our model did not yet include these possibly beneficial effects.

Keywords: cost effectiveness analysis, folic acid, fortified food, health care costs, neural tube defects

Introduction

Folic acid is a vitamin involved in the closure of the neural tube, which occurs in the first weeks after conception when women are generally not aware of their pregnancy. The lack of folic acid with the possible result of improper or partial closure of the neural tube may lead to the development of spina bifida or anencephaly. Therefore, several international organizations, such as the WHO and the FDA, recommend daily intake of 400 µg folic acid around the time of conception.

Due to uncertain risks, the Dutch Health Council advised the government against fortifying food with folic acid, in 2000. Their conclusions were based on uncertain risks suggested in the literature. In particular, the elderly population would be at risk for excess intake of folic acid, which was considered to be highly undesirable. In the USA, flour is generally enriched with 140 µg folic acid per 100 g. The intake of folic acid in the USA increased on average ~190 µg per day in adults, an increase of 30–50%. The increased consumption of folic acid was potentially linked to a relevant reduction in the prevalence of NTDs. In fact, since 1998, the prevalence of NTDs has decreased by 26% in the USA, which may be partially related to the flour fortification. In Canada, a 46–48% decrease in NTDs was seen to coincide with folic acid food fortification.

Despite that half of the Dutch women did consume preconceptional folic acid supplements, the Netherlands could reconsider the decision not to fortify food with folic acid, given these above positive developments in the USA and Canada. In this study, we produced estimations of the costs, savings, health gains, cost-effectiveness and cost-utility for bulk food fortification with 140 µg folic acid per 100 g flour. Estimations were conducted in a base case analysis (presenting the most likely situation) and in sensitivity analysis around the base case assumptions. We applied the societal perspective for our economic analysis, which included the whole spectrum of direct, indirect, medical and non-medical costs.

Methods

Data and assumptions

For the Netherlands, the prevalence of NTDs was estimated at 9/10,000 births, based on data from 1998 to 2000 during which use of folic acid supplements in the advised period (from four weeks before until eight weeks during pregnancy) was 36%. Within the Netherlands, a total number of approximately 200,000 births per year, close to 200 children can be estimated to have been born with an NTD annually during that period. The intake of 400 µg folic acid during the advised period was assumed to reduce the risk for an NTD by ~65% (50% and 80% in sensitivity analysis). For 2005, it was estimated that 51% of the Dutch women use folic acid during the whole period in which folic acid is advised. Therefore, 49% of the women concerned are assumed to have an increased risk to deliver a child with an NTD. This risk could be lowered by implementing a food fortification program.

Health gains

If specific food products were fortified, what would be the proportion of women—not taking supplements—who achieve a sufficient intake from those products to effectively lower the risk? In the absence of any such data, we looked for a proxy indicator that showed a change towards more healthy food.
intake prior to pregnancy. In a 2-yearly questionnaire, distributed via midwives in the Northern and Eastern part of the Netherlands, 11% of the women who did not take supplements indicated that they did consume extra vegetables and fruit while attempting to become pregnant. As these dietary habits may suggest a conscientious attitude amongst women wishing to get pregnant, we assumed that at least these women would get enough folic acid if food was fortified with folic acid (base case assumption at 11% of women not taking supplements; corresponding to 0.11 x 0.49 = 0.051, 5.1% of all women). This estimation is in line with Kelly et al.,12 who estimated a 4.2% increase in women getting enough folic acid due to fortification. Given these data, we performed a sensitivity analysis on the 11% in the base case down to 5% and up to 20% (representing crude halving and doubling of the base case assumption).

For our model, we estimated the unobserved risk for an infant with an NTD in absence of any protection through folic acid (R). To estimate R, we developed and used an algorithm. As a basis, we used the above mentioned prevalence of getting an infant with an NTD at 9/10 000. This corresponded with a percentage of folic acid used of 36% for those women taking supplements in 1998–2000. For those 36% of women taking supplements, the risk factor was assumed to be the unobserved risk factor R, reduced by 65% (0.35 x R). For the remaining 64% of women not taking a supplement, the unobserved risk R would actually apply. By equating the weighted average to the observed risk at 9/10 000, R can be solved:

\[
(0.36 \times 0.35 \times R) + (0.64 \times R) = 0.0009
\]

It follows that \( R = 0.0012 \).

Inserting the estimated \( R \) and the 2005 percentage of use (51%) in the above algorithm results in an estimated prevalence of NTDs in 2005 of 8/10 000. With the total number of newborns in 2005 at 187 910, this corresponds to 148 children born with an NTD. This number is used in the base case. Of those 49% of women who are unprotected—according to the base case—11% will be protected through food fortification; in other words, 7 NTDs out of the 148 can be prevented. In sensitivity analysis 4 and 14 children were assumed to be prevented from NTDs.

**Costs**

Not all children with an NTD need the same types and amounts of care. In particular, care intensity and complexity depends significantly on the exact place of the lesion. A child with a higher located lesion will generally be more disabled and will need more care. The progression-tree for the malformation is shown in figure 1. A child born with an NTD is assumed to have a shorter life-expectancy and lower quality of life than average. Disease specific life-expectancies and age-dependent quality of life estimates are presented in table 1.12–14

Costs were specified and calculated on estimated actual use as presented in table 2. In particular, the total hospital costs included hospital days and surgery. Many infants require liquor-drainage, neural surgery, ultra sounds of the belly and a stoma; exact percentages were found in Staal-Schreinemachers et al.14,15 and the costs in the Dutch guidelines for costing research.14,15 The travel costs for parental hospital visits were estimated based on one assumed visit per day during the child’s hospital stay. The costs for one visit were based on the average distance to the hospital in the Netherlands (7 km) multiplied by the per kilometer costs for traveling by car plus the costs for parking.15 The paramedic costs were calculated based on an expert opinion of the number of physiotherapy consults an infant with NTD needs and the average costs of such a consult. We only calculated physiotherapy costs for the first 18 years, until adulthood. We estimated, based on the literature and expert opinions, the percentages of persons who would need a wheelchair and multiplied them by the average annual costs of using a wheelchair.14,15 The same was done for house adaptations. If the children went to school, they likely needed special education (the numbers were found in Staal-Schreinemachers et al.).14,15 The costs of losses in productivity were inferred from expert opinions of clinical specialists and refer to those losses related to the parents of these children. Furthermore, they were estimated using the Dutch friction costing method, which is the preferred method in the Dutch guidelines for pharmacoeconomic research as they are considered to most closely reflect productivity losses for the Dutch.15

No Dutch information could be obtained on potential costs related to the fortification of bulk food with 140 μg per 100 g flour. The only available information referred to estimations for the US in the early nineties at 5–11 million US dollars.12,16 These amounts were translated into Euros and corrected using Dutch deflators up to 2005.15,17 A crude adjustment for country size was made by using population numbers for the US and the Netherlands.18,19 For the Netherlands, this resulted in estimated costs for folic acid food fortification ranging from €312 000 to €686 000 in 2005. To be conservative, we used the highest estimate in the base case analysis (€686 000). Due to uncertainty regarding this estimate, a broad range

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**Table 1 Life expectancy and quality of life with an NTD**

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Life expectancy (year)</th>
<th>Quality of life</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anencephaly and cervical lesion</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Thoracic lesion</td>
<td>40</td>
<td>0.30</td>
<td>0.18</td>
</tr>
<tr>
<td>Lumbar lesion</td>
<td>72</td>
<td>0.45</td>
<td>0.42</td>
</tr>
<tr>
<td>Sacral lesion</td>
<td>79</td>
<td>0.83</td>
<td>0.73</td>
</tr>
</tbody>
</table>

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**Figure 1** Progression tree [10, 13]
In table 2 all estimated costs due to NTD are shown. Per category, first the costs per unit are estimated (data not shown) and multiplied by the need of that category. This depended on the location of the lesion. After the costs per lesion were calculated, the weighted average lifetime costs for a child with an NTD were determined: €242 948 undiscounted or €128 774 discounted (4%). The quality of life and the life expectancy were included in the weighted average. For example, the costs for one year special education were €14 887 (€74 per school day). School costs are counted from 4 to 16 years of age. We estimated the percentage ‘use of special education’ for each of the four groups: thoracic, lumbar, sacral and anencephaly & cervical as 50%, 46%, 28% and 0%, respectively. The numbers presented in table 2 were found by multiplying (and discounting) above numbers.

In the base case all costs and health gains were discounted at, respectively, 4% and 1.5%, whereas in sensitivity analyses discount rates were varied at 0%, and 4% for health gains and costs.20 All costs were calculated in 2005 values.

Discussion

In our study, folic acid food fortification was estimated to be potentially cost-effective and even cost-saving for most scenarios using conservative estimates for the Dutch situation. Three other studies—including a Dutch study—were conducted to calculate the cost-effectiveness of folic acid to prevent NTDs. In 2001, Postma et al.12 estimated supplemen-
tation folic acid during the recommended period to be cost-effective. In contrast to that study, we applied the societal perspective and we estimated costs for care based on the Dutch situation instead of translating US costs. Two other economic evaluations were conducted for the US. Romano et al.16 and Kelly et al.12 calculated cost-effectiveness for 1991 and 1993, respectively. In our study, we distinguished in severity of the lesion and the level of care, which was also done by Kelly et al.12 In line with our study, above mentioned studies found comparable favourable results: folic acid interventions are largely cost-effective with supplementation estimated at €1750 per LYG for the Netherlands20 and fortification in both US studies estimated to be cost-saving.12,16

In spite of these suggested favourable results, the Dutch Health Council gave a negative advice for bulk food fortification. This was largely due to the risk of high exposure of folic acid in elderly, which may mask a vitamin B12 deficiency, which is in turn associated with a faster decline of cognition. The folate and vitamin B12 status, before and after fortification, is compared in several studies and most studies found an association, but none has systematically addressed this issue.7,21–24 Yet, no significant increase in masked vitamin B12 deficiencies was found in the US after fortification.25

Additionally, a recent Dutch study found epidemiologic evidence suggesting an association between folate, homocysteine levels and hearing levels in elderly.26
Several other effects have been suggested in the literature. In particular, the relationship between folic acid use and cancer needs to be investigated further, with currently both positive and negative effects being suggested. Beneficial effects of folic acid have been suggested for cardiovascular diseases (CVD). After fortification in the US and Canada, the incidence of CVD decreased significantly. Evidence exists primarily on the prevention of NTD in relation to folic acid use, but also the prevalence of other birth defects, such as heart defects, oral clefts, urinary tract defects and limb reduction defects is associated with folic acid use. A weakness of such studies always refers to the power, as it is difficult to find enough cases for such infrequent events. In general, we may note that more research is needed to investigate the effects of folic acid use in the general population, beyond its effects on young women and NTDs. We do note that the potential effects on cancer and CVD have the potential to fastly outweigh the effects on public health (costs) compared to the decline in NTDs. Given the lack of evidence that currently still exists, we were not able to include additional effects beyond the reduction in NTDs in our model.

Some other limitations of our study should be noted. In the calculation of costs and effects, lifetime physical problems (of parents and children), productivity gains of the children and daily care were not taken into account due to difficulties in rendering adequate estimations. Furthermore, we had to crudely translate the enrichment costs from the US to the Netherlands, as Dutch information on this point is lacking.

Europe seems to be conservative compared to Australia, North America and many countries in South America. In these countries the food is mandatory fortified with folic acid. After almost 10 years of enrichment none of the adverse associations described above has been seen in these countries. As the first European country, last year the UK changed its attitude towards mandatory enrichment. In particular, the UK gave initially a negative advice about the enrichment of food with folic acid in 2002. But since then this advice has been reconsidered. On 12 December 2006 the Scientific Advisory Committee on Nutrition advised mandatory folic acid food fortification in the UK to reduce the number of NTDs. Also, the Food Safety Authority of Ireland advised mandatory enrichment in 2006. The UK and Ireland will soon be the first European countries with mandatory food fortification with folic acid implemented.

This situation on the British Isles may serve as an example for next European bodies to adopt fortification, inclusive the Dutch Health Council. This is in particular the case as we illustrated that food fortification is justified also from the economic perspective for the Netherlands, which is potentially also valid for other European countries.

Conclusion

Our model-based study suggests that folic acid food fortification to prevent NTDs may well be cost-effective and even cost-saving for the Netherlands. There is probably more to gain in terms of reductions in other congenital abnormalities and cardiovascular disease, but full evidence is yet lacking. Of possible negative effects, suggested relations with some types of tumors may form the greatest concern. There is need for further research to address this systematically and to achieve consensus on the full scope of effects of folic acid.

Pending a recommendation in favour of food fortification, we advise to invest in public-health interventions aimed to improve the use of folic acid supplements in women with a child wish. All health care professionals—such as obstetricians, GPs, midwives and pharmacists—should be involved in stressing the importance of using folic acid supplements before and during pregnancy.

Acknowledgement

We would like to acknowledge Timothy Broesamle for his useful advice.

Conflicts of interest: None declared.

Key points

- This is the first scientific international publication of the economic evaluation of folic acid food fortification for a European country.
- We estimated that folic acid food fortification may well be cost saving in the Netherlands.
- An economic evaluation for one country in Europe could affect recommendations concerning folic acid food fortification in other European countries.
- Implementation of this, potentially cost-saving, intervention will save new borns from severe disability and or death.

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