Cost-effectiveness of folic acid fortification of flours in prevention of neural tube defects: a scope of the secondary literature

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Contents

Introduction

Neural tube defects (NTDs) represent a group of congenital defects, caused by incomplete closure of the neural tube within 28 days of conception. The most common forms are Anencephaly, Spina Bifida and Encephalocele (NICE 2023). Folic acid deficiency is an important health concern. The fortification of flour with folic acid is considered an effective method for reaching those with pregnancies that are unplanned and those women that do not take folic acid supplements before pregnancy (Gov.Uk 2021). Fortification of maize flour and corn meal with folic acid is recommended to reduce the risk of occurrence of births with neural tube defects (WHO 2016).

The UK government and devolved administrations undertook a public consultation on the proposal to introduce mandatory fortification of UK flour with folic acid. After consideration of the responses received, it intends to proceed with the mandatory fortification of non-wholemeal wheat flour and legislate on that basis, updating and amending The Bread and Flour Regulations 1998 and The Bread and Flour Regulations (Northern Ireland) 1998 (Gov.UK 2021).

The Evidence Service in Public Health Wales was asked to conduct a search into robust secondary sources which answered the question 'What is the cost-effectiveness of folic acid fortification of flours in prevention of neural tube defects?' The purpose of this scoping report is to give an overview of the secondary evidence found related to this question, and to provide high quality research evidence to support further cost-effectiveness analysis that may be undertaken to support the proposed changes.

The findings and conclusions included are those of the source authors and not an interpretation by the Evidence Service. Factors relevant to answering the below question identified from the included systematic reviews have been extracted and briefly summarised within this report. If a specific factor is of interest, it is advisable to read the source from where they were taken in more detail. If utilising any reviews included in this scope to inform policy, it is important to consider the generalisability of their findings to your context. The search undertaken for this scope is unlikely to have identified all evidence relating to this topic, as searches were not exhaustive, but instead focussed on identifying robust systematic reviews.

The question

Table 1: Review question and PICO	
Review question	
What is the cost-effectiveness of folic acid fortification of flours in prevention of neural tube defects?	
Participants	Prenatal, maternal, perinatal and postpartum populations; newborns; populations affected by neural tube defects, such as those with spina bifida (and associated conditions such as anencephaly, meningocele, encephalocele, myelomeningocele and tethered spinal cord syndrome).
Intervention / exposure	Folic acid fortification of flours
Comparison	Standard practice (non-fortification of flours).
Outcomes	Reduction in health care costs associated with neural tube defects
Other Study Considerations	
Systematic reviews; not older than 10 years; based in European countries, excluding USA.	

Key Messages

- Fortification appears to be cost-effective for NTD prevention
- For each monetary unit spent on mandatory folic acid (FA) fortification of flour, there would be a return of 17.5 monetary units
- All folic acid dosages were cost-effective and offered positive health gains, except in one study
- Higher FA dosage was associated with better value for money and higher return of the investment from mandatory FA fortification programs
- Costs associated with mandatory flour fortification include: production, storage, and product distribution to the market, regulatory costs (including national education campaigns and inspection of enriched products) and surveillance of adverse effects on the population
- Associated costs which may be saved by mandatory flour fortification include: caregiver time (hours), reduction in the workforce and productivity, reposition time of workforce (employer), payment of pensions and other social benefits to persons with NTDs; home adequacy and special education.
- The outcomes of two studies showed that FA dosages above 300 µg/100 g have a higher Cost Benefit Analysis (CBA) ratio than FA dosage lower than 300 µg/100 g

Evidence identified which directly addresses the question

Only one systematic review directly addressed the question of cost-effectiveness in using FA fortified flour to prevent neural tube defects (Rodrigues 2021). The aim of this review was to investigate whether mandatory FA fortification of flours is cost-effective as compared to non-mandatory fortification, and to verify whether FA dosage, cost composition, and the quality of economic studies influence the cost-effectiveness of outcomes.

The review results and discussion focussed on three main elements:

- The cost-effectiveness of mandatory flour fortification compared with non-mandatory flour fortification
- Folic acid dosage and cost-effectiveness
- The cost composition of mandatory flour fortification

Thirteen studies were included in the review, with most studies originating in high-income countries (US, Australia, New Zealand, Netherlands), and three coming from middle-income countries (Chile, South Africa and Kazakhstan). No systematic reviews addressing the question were found from the UK or solely from European countries.

In the aforementioned review, eligible studies consisted of original economic analyses of mandatory FA fortification of wheat and corn flours (maize flours) compared to strategies of non-mandatory fortification in flours and/or use of FA supplements for NTD prevention. All of the included studies used the conditions of Spina Bifida and Anencephaly, with the majority also looking at Encephalocele. Six studies in the review looked at the economic benefits of preventing Spina Bifida and Anencephaly over a life-long time horizon, with three studies having a time horizon of 10 to 15 years and the remaining four studies not reporting a time horizon. The outcome of the majority of the included studies was NTD avoided cases and/or the net cost benefit of those avoided cases (n=11). Two studies used the outcomes of quality-adjusted life year (QALY) and years of life lost (YLL).

Cost-effectiveness of mandatory flour fortification

The majority of studies (n=9) compared mandatory fortification with non-fortification or voluntary fortification. The remaining studies (n=4) compared mandatory fortification to dietary supplements of FA or multicomponent comparisons (dietary supplements and campaigns to increase consumption of FA-rich unprocessed food).

The review authors calculated through a cost-effectiveness analysis that, relating the potential benefits of mandatory fortification implementation (avoided costs) to its respective costs (program costs), resulted in a median ratio of 17.1:1. This means that for each monetary unit spent on the program, there would be a return of 17.5 monetary units.

Even in the most unfavourable case to mandatory fortification (an Australian study where the return on investment was 0,98:1) the investment in the program would virtually pay for itself, considering that there would be a ratio of 1 (cost of the program) to 0.98 (avoided costs).

The systematic review examined cost-effectiveness in the included primary studies by looking at the studies' differing analyses. Most of the included studies had a combination of different cost analyses- such as cost-effectiveness analysis (CEA), cost-utility analyses (CUA), cost-benefit (CBA) and cost-utility (CUA). Due to these differences in studies, the review authors analysed the results by subgroups, including FA dosage, cost composition and income difference per country. The types of costs the studies looked at were medical costs, non-medical costs (such as home adaptations) and other costs (such as carers of those with NTDs being absent from the workforce).

Table 2 below provides an overview of the cost benefit results of each included study (Rodrigues et al 2021).

Folic Acid Dosage

The FA dosage varied across the included studies (varying from 100 µg to 700 µg per 100 g of flour) but the most frequent quantities were 140 µg and 200 µg folic acid per 100 g of flour.

The outcomes of two studies showed that FA dosages above 300 µg/100 g have a higher cost-benefit ratio to FA dosage when compared to FA dosages below 300 µg/100 g. Notably, all FA dosages were cost-effective and offered positive health gains, except in one study from Australia.

The review authors concluded that there is lack of evidence about which FA dosage is more cost-effective. This aspect is particularly relevant in the context of high heterogeneity in FA dosage among mandatory fortification programs across the world. The review authors state that their findings are in line with results from the wider literature, since in the review, higher FA dosage was associated with better value for money and higher return of the investment from mandatory FA fortification programs.

Cost Composition

The review did not report detailed quantitative results, but instead described the cost composition of varying associated costs of mandatory fortification of flour and potential indirect costs associated with NTDs.

Several of the included primary studies described direct costs for the private sector and public sector. For milling industries, the studies attributed costs of production, storage, and product distribution to the market. The regulatory costs of mandatory flour fortification included national education campaigns and inspection of enriched products. Four studies included the costs of surveillance of adverse effects on the population.

Most studies did not report on cost-effectiveness in terms of indirect costs. Seven studies included calculation variables such as caregiver time (hours), reduction in the workforce and productivity, reposition time of workforce (employer), payment of pensions, and other social benefits to persons with NTDs. The most frequent non-medical cost composition in the studies were home adequacy, special education, and the time (hours) caregivers dedicated to patients. Only one study included travel costs for parents during patients' hospitalisation.

One study suggested that the loss of consumer choice should be considered as a cost for the population, even when there is another option of flour (fortifier-free) because the choice will remain restricted. The method consisted of attributing a value in U.S. dollars (US$ 1) to this loss, affecting thousands of people who do not belong to the target population of the intervention, substantially increasing the cost of mandatory fortification.

Although the studies in this review presented cost-effective outcomes with fortification in NTD prevention, only six studies showed that fortification was also cost saving. In these studies the direct costs refer only to the fortification process and NTD treatment, except for two studies that included non-medical costs (home layout adequacy and special education). Other studies may have been cost-effective rather than cost saving as they added different variables to direct costs, such as national education/awareness campaigns for the target population and training of professionals, which would likely include substantial spending on national education campaigns.

Considerations and Limitations

No current systematic reviews were found from the robust secondary sources used by the Evidence Service. Therefore, critical appraisal was undertaken on the only systematic review, found in a search of the database Medline, using the Evidence Service's critical appraisal tool for systematic reviews. The full critical appraisal can be provided by the Evidence Service upon request. The systematic review was appraised as being as of an acceptable quality. Our assessment identified that the review was well conducted, because authors reported the search according to PRISMA, undertook quality appraisal using a relevant tool and considered relevant outcomes. Authors also outlined their comprehensive search of the literature and clearly outlined the inclusion criteria. However, it was unclear if the quality assessment included consistency checks by a second reviewer, but they did reflect on the quality of included primary studies in the discussion. Further information on relevant comments and caveats related to the critical appraisal of the review can be found in the data extraction table below (**Table 3**).

The quality assessment of included primary studies varied, but the majority (n=7) were deemed to be of medium to high quality by the review authors, using the Drummond tool,

Three primary studies used estimates of NTD reduction from the U.S. The adopted perspective was that of society; however, four primary studies did not inform a perspective and in two, it was not possible to identify the perspective. The time horizon was the expected lifetime for persons with Spina Bifida and Encephalocele, and three primary studies adopted a period of 10 to 15 years. The others did not inform a time horizon or it was not possible to identify it.

The thirteen included studies within the systematic review varied in their countries of origin, healthcare systems, FA dosage, and in their comparators to mandatory FA fortification, (comparators included non-fortification, voluntary fortification and dietary awareness programmes). Results from these countries may not be generalisable to the UK.

The interventions varied between studies, reflecting the diversity of local regulations on mandatory fortification programs in terms of FA dosage. The authors report that it was not possible to conduct a comparison of outcomes in the economic assessments owing to differences in the measures of benefits, perspectives, time horizon, and currency. Due to the differences between the pharmacoeconomic guidelines of the countries, there was variability in cost composition, calculation methodology, and discounts in the studies.

There was no comparable measure of investment returns between studies, so when the return of investment was not available in the included studies, the review authors

calculated it by dividing total cost averted attributed to mandatory FA fortification by the total cost of the mandatory FA fortification program.

Six primary studies were conducted before fortification of flours; therefore, the outcomes of these economic evaluations could be underestimated. The majority of studies (n=7) were from the post-fortification stage.

Next steps

As only one systematic review was identified which was directly relevant to the question, it may be appropriate to conduct a scoping review of primary literature to identify other research which addresses this question, particularly primary research from the UK or Europe if available.

Sources searched

Cochrane database of systematic reviews - https://www.cochranelibrary.com/cdsr/reviews *Systematic reviews on health care interventions, diagnostics and public health interventions.*
NICE - https://www.nice.org.uk/guidance *Guidelines of health care and public health topics. Note: you should be looking for systematic evidence reviews that may underpin guidance on your topic, not the guidance itself. Not all recommendations are based on evidence reviews.*
Joanna Briggs Institute -https://journals.lww.com/jbisrir/pages/advancedsearch.aspx *This organisation's journal, JBI Evidence Synthesis includes systematic and scoping reviews of both quantitative and qualitative evidence on healthcare and public health topics.* *Search using your keywords AND "systematic review"*
Prospero - https://www.crd.york.ac.uk/prospero/ *Always check this database of systematic review protocols to see whether an up to date systematic review related to your question is in progress.* *You will only need to look at the most recent protocols (last two years) as earlier protocols should have been published and will be found in other sources.*
National Institute for Health Research (NIHR) Public Health Research - https://www.journalslibrary.nihr.ac.uk/phr/about-the-phr-journal.htm *Some reports in this journal are systematic reviews of interventions to improve public health.*
The Evidence for Policy and Practice Information and Co-ordinating Centre (EPPI-Centre) - http://eppi.ioe.ac.uk/cms/ *Check the publications list for systematic reviews in the fields of education, health promotion and public health, as well as social welfare and international development.*
Campbell Collaboration systematic reviews -https://www.campbellcollaboration.org/better-evidence.html

Systematic reviews of the effects of social interventions in Crime & Justice, Education, International Development, and Social Welfare.
What Works Centre for Wellbeing - https://whatworkswellbeing.org/about-us/ *Systematic reviews of the impacts of policies and projects on wellbeing.*
What Works for Children's Social Care - https://whatworks-csc.org.uk/ *Systematic reviews relevant to children's social care.*
Early Intervention Foundation (EIF) - https://www.eif.org.uk/about *Systematic reviews about early interventions for tackling the root causes of social problems for children and young people.*
Health Technology Wales - https://healthtechnology.wales/ *Reports and guidance on use of medical devices, surgical procedures, psychological therapies, tele-monitoring or rehabilitation.*
Health Technology Assessments (Ireland) - https://www.hiqa.ie/areas-we-work/health-technology-assessment *Health technology assessments on the clinical and cost-effectiveness of drugs, equipment, diagnostic techniques and public health activities.*
National Institute for Health Research Health (NIHR) Technology Assessment (HTA) Journal - https://www.journalslibrary.nihr.ac.uk/hta/about-the-hta-journal.htm *Some reports in this journal are systematic reviews of interventions to, prevent and treat disease and improve rehabilitation and long-term care.*
Agency for Healthcare Research and Quality (AHRQ) Search Evidence-Based Reports | Agency for Healthcare Research and Quality (ahrq.gov) *Effectiveness and comparative effectiveness reviews of health care interventions.*
Canadian Agency for Drugs and Technologies (CADTH) - https://www.cadth.ca/evidence-bundles-view *Rapid response systematic reviews and meta-analyses of health technologies, including drugs and diagnostic tests, medical, dental and surgical devices and procedures.*
Evidence Synthesis Program Reports (va.gov) - https://www.hsrd.research.va.gov/publications/esp/reports.cfm *Evidence syntheses of health care interventions of particular relevance to veterans.*
Scottish Intercollegiate Guidelines Network (SIGN) clinical guidelines - https://www.sign.ac.uk/our-guidelines/ *Clinical practice guidelines. Note: you should be looking for systematic evidence reviews that may underpin guidance on your topic, not the guidance itself. Not all guidance is based on evidence reviews*

Additional sources searched
Google Scholar – https://scholar.google.com/ *Search using your keywords AND "systematic review"*

Medline – https://www.scopus.com/search/form.uri?display=basic#basic *Search using your keywords AND [Systematic Review]*

Search terms

A search was conducted using a combination of the following terms:

- "Neural Tube Defects"
- "Folic acid"
- "Flour"
- "Cost"/ "Cost-effectiveness"

Table 2: Overview of studies and cost benefits

Author Country Year	Type of Study	Time Horizon	Mandatory Fortification (acid folic/ flour)	Comparison strategies	Health Outcomes	Disease Conditions	Results
Romano USA 1995 Pre-fort	CBA	Not reported	140 mcg/100 g 350 mcg/100 g	Dietary supplement	NTD avoided cases	Spina bifida Anencephaly Neuropathy	Net economic benefits 4.3:1 (140mcg) and 6.1:1 (350 mcg)
Bagriansky Kazakhstan 2003 Pre-fort	CBA	10 years	Not reported	Non-fortification	Net benefit	Spina bifida Anencephaly Heart disease	10-Year Benefit Ratio is 11.7 with an Internal Rate of Return estimated at 319%
Grosse USA 2005 Post-fort	CEA/ CUA	Not reported	140 mcg	Non-fortification	Avoided NTD births and net benefit	Spina bifida Anencephaly	The cost savings (net reduction in direct costs) were estimated to be in the range of $88 million to $145 million per year.
FSANZ Aus/New Zealand 2006 Pre-fort	CBA	15 years	100 mcg/100 g 200 mcg/100 g	Voluntary fortification	Net benefit (avoided DALYs) Avoided costs	Spina bifida Anencephaly and Encephalocele	In both Australia and New Zealand, the benefits of mandatory fortification of all bread making flour with folic acid outweigh the costs.
Llanos Chile 2007	CEA/ CUA	Not reported	200 mcg/100 g	Non-fortification	Avoided fetal deaths	Spina bifida Anencephaly	Considering averted costs of care, fortification resulted in net cost savings of I$ 2.3 million

Author Country Year	Type of Study	Time Horizon	Mandatory Fortification (acid folic/ flour)	Comparison strategies	Health Outcomes	Disease Conditions	Results
Post-fort					Avoided DALY Avoided NTDs		
Jentink Netherlands 2008 Pre-fort	CEA/ CUA	Life-long	140 mcg/100 g	Non-fortification Voluntary fortification	QALY, YLL	Spina bifida	Our model suggests that AF fortification of bulk food to prevent cases of NTD in newborns might be a cost-saving intervention in the Netherlands.
Sayed South Africa 2008 Post-fort	CBA	Not reported	Wheat flour 1.5 mg/kg Corn flour 2.21 mg/kg	Non-fortification	Avoided NTD costs	Orofacial clefts and Spina bifida.	The cost benefit ratio in averting NTDs was 46 to 1.
Bentley USA 2009 Post-fort	CEA/ CUA	Life-long	140 mcg/100 g 300 mcg/100 g 700 mcg/100 g	Non-fortification	QALY	Spina bifida, Anencephaly Heart attack, Colon cancer Masking of Vit B12 deficiency	Compared with no fortification, all post-fortification strategies Provided QALY gains and cost savings for all subgroups.
Dalziel Aus/New Zealand 2009 Pre-fort	CEA/ CUA	CEA 10 years CUA Life expectancy 80 years	200 mcg/100 g 135 mcg/100 g	National program promoting: 1) dietary supplement use. 2) voluntary fortification extension. 3) campaign to	Avoided NTD cases Avoided DALY	Spina bifida Encephalocele	Mandatory fortification was not cost-effective for New Zealand at $AU 138,500 per DALY ($US 109,609, £56,216), with results uncertain for Australia, given widely varying cost estimates.

Author Country Year	Type of Study	Time Horizon	Mandatory Fortification (acid folic/ flour)	Comparison strategies	Health Outcomes	Disease Conditions	Results
				increase consumption of FA-rich unprocessed food.			
Rabovskaja Australia 2013 Pre-fort	CEA/ CUA	Life-long	Bread flour: 200 mcg/100 g	Voluntary fortification	QALY years of life; avoided NTD cases	Spina bifida Anencephaly Neuropathies	Mandatory fortification was cost-effective at A$10,723 per LYG and at A$11,485 per QALY. However, inclusion of the loss of consumer choice can change this result.
Grosse USA 2016 Post-fort	CBA	Life-long	140 mcg/100 g	NTDs prevalence pre and post- fortification	Net benefit	Spina bifida Anencephaly	Fortification with folic acid is effective in preventing NTDs and saves hundreds of millions of dollars each year.
FSANZ Australia 2017 Post-fort	CBA/ CEA/ CUA	Lifetime 82.3 years (maximum)	Bread flour: 200 mcg/100 g	Non-mandatory fortification	Avoided NTD cases; years of life; QALY	Spina bifida Anencephaly Encephalocele	Mandatory fortification was cost-effective, equitable, and efficient in comparison with the set of pre-mandatory fortification policies.
Saing Australia 2019 Post-fort	CEA/ CUA	Lifetime 78 years	200 mcg/100 g	Voluntary FA Fortification of flours (including education and supplementation programs).	QALY; years of life; avoided NTD cases.	Spina bifida Anencephaly Encephalocele	Mandatory folic acid fortification (in addition to policies including advice on supplementation and education) improved equity in certain populations and was effective and highly cost-effective for the Australian population.

Table 3: Secondary sources of interest identified

Systematic reviews

Reference	Aim/Question	Abstract or summary	Comments
Rodrigues, V.B et al. (2021). Cost-effectiveness of mandatory folic acid fortification of flours in prevention of neural tube defects: A systematic review. PLOS ONE 2021 Vol. 16 Issue 10 Pages e0258488.DOI:10.1371/journal.pone.0258488 https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0258488#sec026	To investigate whether mandatory folic acid (FA) fortification of flours is cost-effective as compared to non-mandatory fortification, and to verify whether FA dosage, cost composition, and the quality of economic studies influence the cost-effectiveness of outcomes.	The review included 13 studies from seven countries. Four were high-income countries (US, Australia, New Zealand, Netherlands), and three were from middle-income countries (Chile, South Africa and Kazakhstan). Five of the seven included countries are OECD members. In the review, eligible studies consisted of original economic analyses of mandatory folic acid (FA) fortification of wheat and corn flours (maize flours) compared to strategies of non-mandatory fortification in flours and/or use of FA supplements for NTD prevention. The outcome of the majority of the included studies was NTD avoided cases and/or the net benefit of those avoided cases (11 studies). Two studies used the outcomes of quality-adjusted life year (QALY) and years of life lost (YLL). Results of a cost-effectiveness analysis showed that fortification is cost-effective for NTD prevention, except for in one study in New Zealand. The cost-benefit analysis yielded a median ratio of 17.5:1	Population characteristics of included studies are not individually described. The review authors state in general the populations are women of childbearing age (10 to 45 years old) of any ethnic group and populations with NTDs. Most (7 of the 13) included studies reported objective economic outcomes, such as net benefit or costs of averted care. 4 studies reported outcomes of: LYG (life years gained); DALY (disability-adjusted life years); QALY (quality adjusted life years). It was not possible to conduct a comparison of outcomes in the economic assessments owing to differences in the measures of benefits, perspectives, time horizon, and currency. The variability in cost composition, calculation methodology, and discounts in the studies can be attributed to the differences between the pharmacoeconomic guidelines of the countries.

		(0.98:1 to 417.1:1); meaning that for each monetary unit spent in the program, there would be a return of 17.5 monetary units. All FA dosages were cost-effective and offered positive health gains, except in one study. The outcomes of two studies showed that FA dosages above 300 µg/100 g have a higher CBA ratio. The studies with the inclusion of “loss of consumer choice” in the analysis may alter the fortification cost-efficacy ratio.	In general, the studies were of medium to low quality, although some used international methodological patterns in economic assessments. Some studies were based on data from observational studies, which may jeopardize the reliability of outcomes. Most of the population databases were from the post-fortification stage. Only Chile and New Zealand have free at the point of contact healthcare, with the other countries either requiring private insurance or comprising a mix of public and private care. Therefore, the results may not be generalisable to Wales and the NHS. The production and consumption of flour and the rate of occurrence of NTDs may differ in Wales and the UK as opposed to the other countries and this should be examined in greater detail.

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