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Folic acid to reduce neonatal mortality from neural tube disorders

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Background Neural tube defects (NTDs) remain an important, preventable cause of mortality and morbidity. High-income countries have reported large reductions in NTDs associated with folic acid supplementation or fortification. The burden of NTDs in low-income countries and the effectiveness of folic acid fortification/supplementation are unclear.

Objective To review the evidence for, and estimate the effect of, folic acid fortification/supplementation on neonatal mortality due to NTDs, especially in low-income countries.

Methods We conducted systematic reviews, abstracted data meeting inclusion criteria and evaluated evidence quality using adapted Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology. Where appropriate, meta-analyses were performed.

Results Meta-analysis of three randomized controlled trials (RCTs) of folic acid supplementation for women with a previous pregnancy with NTD indicates a 70% [95% confidence interval (CI): 35–86] reduction in recurrence (secondary prevention). For NTD primary prevention through folic acid supplementation, combining one RCT with three cohort studies which adjusted for confounding, suggested a reduction of 62% (95% CI: 49–71). A meta-analysis of eight population-based observational studies examining folic acid food fortification gave an estimated reduction in NTD incidence of 46% (95% CI: 37–54). In low-income countries an estimated 29% of neonatal deaths related to visible congenital abnormalities are attributed to NTD. Assuming that fortification reduces the incidence of NTDs, but does not alter severity or case-fatality rates, we estimate that folic acid fortification could prevent 13% of neonatal deaths currently attributed to congenital abnormalities in low-income countries.

Discussion Scale-up of periconceptional supplementation programmes is challenging. Our final effect estimate was therefore based on folic acid fortification data. If folic acid food fortification achieved 100% population coverage the number of NTDs in low-income countries could be approximately halved.

Conclusion The evidence supports both folic acid supplementation and fortification as effective in reducing neonatal mortality from NTDs.

Keywords Neonatal mortality, folic acid, neural tube defects, pregnancy, infant, newborn, Neural Tube Defects/mortality/prevention & control, dietary supplements

Background

Neural tube defects (NTDs) are congenital malformations of the brain and spinal cord caused by failure of the neural tube to close between 21 and 28 days following conception. Defects range from anencephaly, through encephalocoeles to spina bifida, which is more variable in severity and effect (Table 1). Anencephaly is invariably associated with death as a stillbirth, a neonatal death or occasionally a post-neonatal death. Encephalocoele and spina bifida may be associated with neonatal death, infant death or with impairment which is frequently severe in the absence of surgery—e.g. lower limb paralysis, incontinence, convulsions and frequent central nervous system (CNS) infections. Even with surgery to close the spinal defect and insert ventriculo-peritoneal shunts, spina bifida is associated with premature mortality and a high degree of disability.[1] Less severe defects include spina bifida occulta. Whilst these can have long-term neurological sequelae, they rarely cause neonatal death. This article therefore focusses on livebirths with open NTDs. It should, however, be noted that in countries with antenatal ultrasound (USS) available, the true effect of folic acid on preventing affected foetuses will be underestimated.

NTDs are an important cause of mortality and morbidity globally with a conservative estimated incidence of >300 000 new cases a year[2] resulting in an estimated 41 000 deaths and 2.3 million disability-adjusted life years (DALYS).[3] They thus comprise about one-tenth of the burden of all congenital conditions and constitute the third largest congenital burden after congenital heart disease and Down's syndrome.[3]

Over 95% of all NTDs are first occurrence, with a small proportion being repeat events in women with a previously affected pregnancy.[6] Risk factors include genetic factors (which may explain the high prevalence in certain populations, e.g. in Ireland and some provinces in China), environmental factors, particularly folic acid deficiency at the time of conception, diabetes and obesity. In most studies from countries where a folate-rich diet is not available to

Table 1 Categories of neural tube defects, their features and sequelae[4–5]

	Anencephaly	Encephalocoele	Spina bifida cystica
Cause	Failure of closure of the anterior (cranial) neural arch	Failure of closure of the anterior (cranial) neural arch at a later stage of embryogenesis than anencephaly	Failure of closure of the posterior (caudal) vertebral arch. Most commonly affecting the lumbo-sacral region and usually associated with hydroecephalus (blockage of drainage of the cerebrospinal fluid)
Clinical features	Absence of variable amounts of brain, spinal cord, nerve roots and meninges	Sack containing brain tissue herniates through midline skull defect, usually occipital	Herniation of the meninges through a defect in the lower spine (meningocoele) or severe forms include also herniation of dysplastic spinal cord (myelomeningocoele) Hydrocephalus resulting in extra fluid around the brain and raised intracranial pressure.
Prognosis and sequelae	Stillbirth or neonatal death	Variable–high mortality from meningitis. With surgical repair long-term outcome varies from normal function to severe multi-domain impairment	Variable levels of disability including: *Neurological*: sensory and motor defects, learning disabilities, epilepsy. *Orthopaedic:* contractures, joint dislocation, talipes. *Functional:* bladder and bowel dysfunction.

all, NTDs exhibit a social gradient with the most economically disadvantaged in a population having the highest incidence.[7–10] Even in high-income countries, lower maternal education status is associated with higher risk of NTDs.[8,11]

Over the past decades many countries have reported a reduction in prevalence at birth of NTDs.[12] In one series an overall 93% decrease in prevalence at birth was accounted for by a combination of second-trimester screening and termination of affected pregnancies (34%) and an underlying decrease in the prevalence of affected conceptions (59%), in part explained by folic acid supplementation.[13] The role of periconceptional folic acid in the prevention of NTDs has been investigated since the 1980s. High-quality evidence, particularly from randomized controlled trials (RCTs) in Hungary which showed a reduction in recurrent NTDs with folic acid supplementation,[14] led to many high-income countries adopting policies recommending supplementation for women planning pregnancy.[15] Commonly, this involved recommending a 0.4 mg folic acid tablet daily to all women planning pregnancy and 4 mg folic acid to those with a previous pregnancy affected by NTDs.

A successful periconceptional folic acid supplementation programme requires a high proportion of pregnancies to be planned as well as easy access to a functioning health system and effective local social marketing interventions.[16] However, unplanned pregnancies may account for one-third to one-half of all pregnancies even in high-income settings[17,18] and thus supplementation policies have had limited impact at a population level, even in high-income countries.[19] The public health impact of folic acid supplementation is likely to be lower in low-income countries where unplanned pregnancies are more common and access to, and cost of, folic acid are greater barriers.

Another option for ensuring increased folic acid intake around the time of conception is folic acid fortification of food. Interest in this approach has increased recently and it has been implemented in 57 countries to date.[20] In many cases the fortification policy is driven by the food industry. However, the effectiveness of fortification is dependent on dietary norms—e.g. flour fortification may be ineffective in some South Asian and African countries if many families, especially the poor who are most at risk, do not regularly eat purchased flour products.

A recent US Preventive Services review has examined the growing evidence that folic acid supplementation in high-income countries provides benefit in reduction of risk for first NTDs.[21] Our study provides a quantitative estimate of the effect folic acid on the reduction in risk using evidence for folic acid fortification and supplementation.

Objective

The objective of this article is to estimate the effect of folic acid on neonatal mortality from NTDs in low-income countries, and hence to estimate the proportionate mortality reduction for visible congenital abnormalities. This estimate of effect will facilitate country-specific analysis using the LiST tool to estimate reductions in numbers of neonatal deaths.

Methods

We systematically reviewed the published literature to identify studies of periconceptional folic acid use (supplementation or fortification) for the prevention of neonatal NTDs mortality and morbidity on 24 February 2009 and an updated search was performed on 13 September 2009. We searched PubMed, EMBASE, Cochrane Libraries and all World Health Organization Regional Databases and included publications in any language.[22] Snowball searching was used whereby literature referenced in key papers was included. Combinations of the following search terms were used: 'neural tube defect', 'neonatal mortality/morbidity', 'folic acid', 'pregnancy', 'newborn, infant' (Figure 1).

Inclusion/exclusion criteria

We applied the Patient, Intervention, Comparison, and Outcome (PICO) format to define the studies to be included as follows. The 'population' of interest were neonates and the 'interventions' being reviewed were the effect of folic acid supplementation (using folic acid tablets 0.36 mg once daily to 5 mg once a week) or of food fortification with folic acid. The comparison group were those neonates born after pregnancies without folic acid fortification or supplementation. The outcomes of interest were NTDs and mortality associated with NTDs (Table 1). In this study, we considered both randomized trials and observational studies meeting these criteria (Figure 1). We excluded studies not fulfilling the inclusion criteria and any duplicate reports of trials or studies. Possible adverse effects of folic acid supplementation and fortification were not addressed as part of this review.

Abstraction, analyses and summary measures

All studies meeting the inclusion criteria were abstracted onto a standardized abstraction form for each outcome of interest.[22] Each study was assessed and graded according to the Child Health Epidemiology Reference Group (CHERG) adaptation of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) technique.[23] The evidence was summarized by outcome including a qualitative assessment of study quality and sources

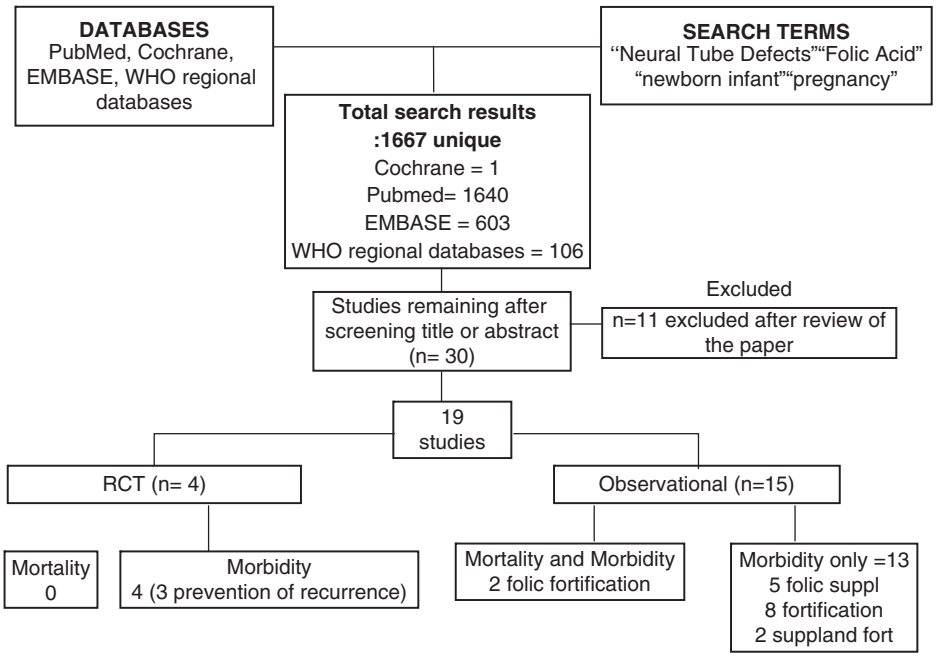

Figure 1 Synthesis of study identification in the review of the effect of folic acid on neonatal mortality form neural tube disorders. Detailed Pubmed search terms: ("folic acid"[MeSH Terms] OR ("folic"[All Fields] AND "acid"[All Fields]) OR "folic acid"[All Fields]) AND ("neural tube defects"[MeSH Terms] OR ("neural"[All Fields] AND "tube"[All Fields] AND "defects"[All Fields]) OR "neural tube defects"[All Fields] OR ("neural"[All Fields] AND "tube"[All Fields] AND "defect"[All Fields]) OR "neural tube defect"[All Fields]) AND ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "neonate"[All Fields]) OR ("infant mortality"[MeSH Terms] OR ("infant"[All Fields] AND "mortality"[All Fields]) OR "infant mortality"[All Fields] OR ("neonatal"[All Fields] AND "mortality"[All Fields]) OR "neonatal mortality"[All Fields]) OR ("women"[MeSH Terms] OR "women"[All Fields] OR "female"[MeSH Terms] OR "female"[All Fields] OR "pregnancy"[MeSH Terms] OR "pregnancy"[All Fields] OR periconceptual[All Fields] OR "peri conceptual"[All Fields]) Embase/ WHO regional databases: 'neural tube defects' 'folic acid'

of bias as adapted from the Cochrane review handbook. Evidence from low/middle-income countries was assessed separately based on the World Bank classification of income groups. CHERG Rules for Evidence Review were applied to the collective evidence to provide an estimate for reduction in neonatal NTD mortality.

Separate meta-analyses were planned for folic acid supplementation effect on secondary and primary prevention, as well as a third meta-analysis of the effect of folic acid fortification. Meta-analyses were conducted with STATA version 10 statistical software.[24] Heterogeneity was assessed using chi-square test. When evidence of heterogeneity was present ($P < 0.10$), a random effects model was used, otherwise a fixed effect was assumed. Appropriate summary risk ratios and corresponding 95% confidence interval (CI) are reported.

Results

The search strategy from all listed databases identified 1667 records (Figure 1). After initial screening of the title or abstract we reviewed 30 papers for the outcome measures of interest. Nineteen papers were included in the final database (Supplementary Table 1 available at *IJE* online). One relevant Cochrane Review of periconceptional folic acid supplementation was available.[25] This review combined, in one meta-analysis, three trials to prevent recurrence of NTDs with one RCT of folic acid supplementation for prevention of first occurrence of NTDs.

(i) *Prevention of the recurrence of neural tube defects:* We identified three RCTs of the effect of folic acid supplementation on the risk of recurrence of NTDs in women with previously affected pregnancies.[26–28] A meta-analysis of these three trials resulted in a risk ratio (RR) of 0.30 (95% CI: 0.14–0.65; Figure 2a) However, of greater interest from a public health perspective, is prevention of first occurrence.

(ii) *Prevention of first occurrence of neural tube defects through supplementation:* Eight studies of the effect of folic acid supplementation on incidence of first occurrence of NTDs were identified. No randomized trials of folic acid supplementation reported the effect on neonatal mortality.

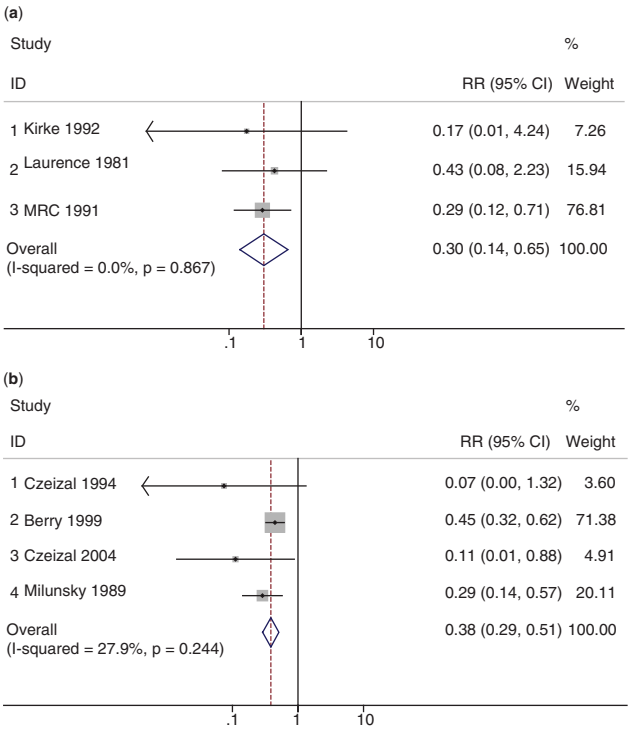

Figure 2 Meta analysis of the effect of folic acid supplementation. (**a**) Prevention of recurrent neural tube disorders (secondary prevention), Relative Risk (95% Confidence Interval); Heterogeneity $\chi^2 = 0.28$ (degrees of freedom (df = 2) $P = 0.867$, I^2 (variation in RR attributable to heterogeneity) = 0%, Test of RR = 1: $z = 3.06$, $P = 0.002$. (**b**) Primary prevention of neural tube disorders, Relative Risk (95% Confidence Interval), Heterogeneity $\chi^2 = 4.16$ (df = 3) $P = 0.244$, I^2 (variation in RR attributable to heterogeneity) = 27.9%, Test of RR = 1: $z = 6.59$, $P < 0.001$

Four before-and-after studies of education campaigns, which all achieved coverage of folic acid supplementation of <50%, were excluded.[29–32] There was not strong evidence of heterogeneity between the remaining four studies (one RCT[14] and three cohort studies which adjusted for confounding;[33–35] $P = 0.24$; $I^2 = 27.9\%$). A meta-analysis of these four studies produced an estimated risk ratio for the effect of folic acid supplementation on the incidence of NTDs of 0.38 (95% CI: 0.29–0.51; Figure 2b). Further evidence that folic acid supplementation protects against NTDs is provided by four case–control studies which reported reductions in the incidence of NTDs with folic acid supplementation (0.4–0.8 mg) ranging from 35 to 75%.[36–39] Including the four studies with poor coverage in the meta-analysis resulted in an estimate of 0.63 (95% CI: 0.48–0.82). This lower estimate of effect is likely to reflect the difficulty of achieving high coverage of a supplementation programme. (see Supplementary Figure 1 available at *IJE* online).

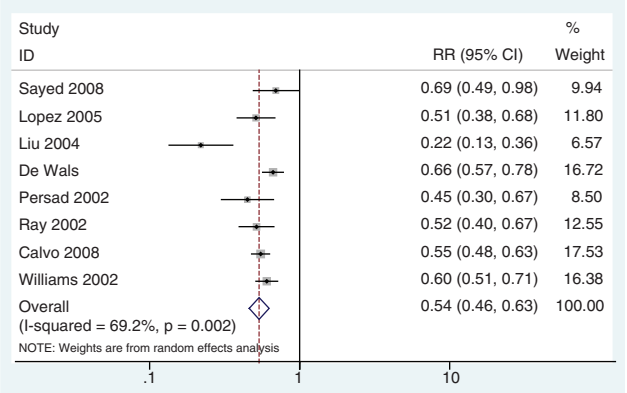

Figure 3 Meta-analysis (random effects) of the effect of folic acid fortification on primary prevention of neural tube defects. Heterogeneity $\chi^2 = 22.73$ (df = 7), $P = 0.002$, I^2 (variation in RR attributable to heterogeneity) = 69.2%; Estimate of between-study variance $\tau^2 = 0.0295$, Test of RR = 1: $z = 8.01$, $P < 0.001$

(iii) *Primary prevention of neural tube defects through fortification:* Ten before-and-after studies assessing the effect of mandatory folic acid fortification on the incidence of NTDs were also abstracted. One study was excluded[40] as it was performed in a setting with routine antenatal ultrasound screening for congenital abnormalities, high numbers of terminations of affected pregnancies and reported only birth certificate data. Eight of the remaining studies from Chile,[41] South Africa,[42] Argentina,[43] USA[44] and Canada[31,32,45,46] showed evidence of heterogeneity ($P = 0.002$; $I^2 = 69.2\%$). A random-effects meta-analysis of all eight studies produced an estimated risk ratio of 0.54 (95% CI: 0.46–0.63; Figure 3). The heterogeneity observed appears to be largely attributable to one of the Canadian studies.[31] If this study is excluded from the analysis there is no longer strong evidence of heterogeneity ($P = 0.26$; $I^2 = 22.8\%$). The risk ratio is little changed (0.58). The outlying study was relatively small, with a high baseline rate of NTDs (4.4/1000) compared with the other studies, but was otherwise unexceptional. Restricting the analysis to the three studies from middle-income countries[28,41–43] produced little change in the estimated risk ratio (0.56; (95% CI: 0.50–0.63). These results are consistent with the final study retrieved of vital registration data from Oman reporting a 62% reduction in NTDs incidence (from 1.6 to 0.6 per 1000 live births) after folic fortification; this study was excluded from the meta-analysis as no detailed point estimate or numbers of cases were reported.[47] Sensitivity analyses indicate little difference in the estimates using the different inclusion criteria and meta-analysis methods (Figure 4).

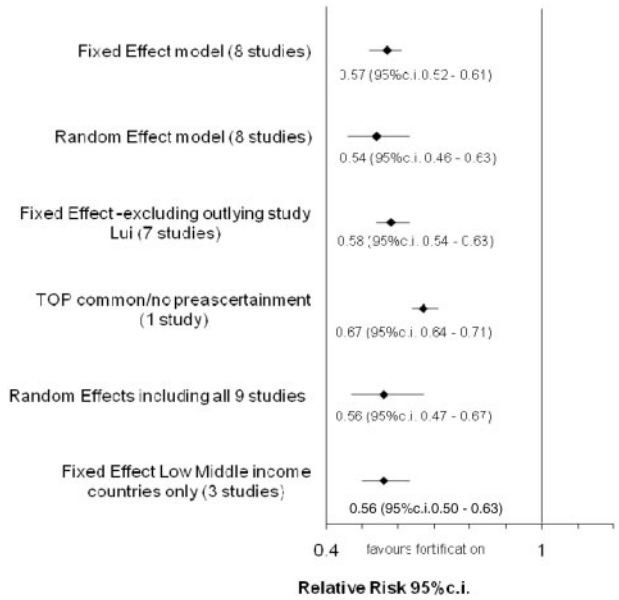

Figure 4 Sensitivity analyses of the estimate of the effect folic acid fortification using different inclusion criteria and meta-analysis methods

Quality of the evidence

The CHERG Rules for Evidence Review were applied[22] (Table 2). The observed reduction in NTDs with folic acid fortification or supplementation was large and fairly consistent across the different study designs and, indeed, between supplementation and fortification. There is high-quality evidence for the effect of periconceptional folic acid on occurrence of recurrent NTDs with an estimated reduction of 70% (95% CI: 35–86) but this is not the question of primary interest for public health implementation.

In terms of direct cause-specific mortality evidence, there is low-quality evidence for a cause-specific mortality reduction from one large before-and-after study of folic acid fortification of 360 994 births in Argentina.[43] This study reports a 57% reduction in neonatal mortality from NTDs after the introduction of folic acid fortification. In addition, one study from South Africa (808 661 births) reported a 66% reduction in perinatal mortality with folic acid fortification.[42] None of the higher quality trials addressed the impact of folic acid on reducing mortality from NTDs.

Our new meta-analysis for primary prevention of NTD using folic acid supplementation suggests an estimated reduction in primary occurrence of 62% (95% CI: 49–71). We grade this evidence as moderate quality, based on one RCT and three cohort studies that are consistent, together with the high quality evidence for a reduction in recurrence of NTDs.

Evidence for a protective effect of folic acid food fortification comes from eight large before-and-after population-based studies including 3047 cases of NTDs. The estimated risk reduction associated with food fortification is 46% (95% CI: 37–54). While the studies are of low quality, the evidence grade allocated is moderate since there are eight studies which are very consistent and there is strong biological plausibility based on the supplementation trials. Assuming that folic acid has no effect on the ratio of anencephaly to other spinal defects, and that the case-fatality rates remain constant, the reduction in mortality from NTDs would be equal to the reduction in occurrence, i.e. 46%.

Estimation of the effect of folic acid food fortification on neonatal deaths due to congenital causes in low-income settings

The LiST tool is a tool which enables health planners in low-income countries to investigate the likely effect on maternal, neonatal and child mortality of different policy options. Within the tool the number of neonatal deaths attributed to congenital causes is estimated using a statistical model using mainly verbal autopsy data as inputs. A major weakness of this approach is that only deaths in newborns with visible congenital malformations will be attributed to congenital causes. For example, deaths due to congenital heart disease will be misclassified. NTDs represent a high proportion of deaths due to visible congenital malformations. Current global estimates for the number of neonatal deaths due to congenital causes by region are based on methods described previously[48] (Table 3). Work in progress for the Global Burden of Disease provides estimates of the number of neonatal deaths due to NTDs by region (Table 3). The median percent of congenital abnormalities attributed to NTDs is 29%. A 46% reduction in NTD deaths would, therefore, be expected to reduce the number of deaths due to visible congenital malformations by 29% × 46%, i.e. 13%.

Discussion

NTDs remain an important yet potentially preventable cause of neonatal mortality. Dietary change and selective termination of affected pregnancies has resulted in severe NTDs rarely being seen in high-income countries. Data from three randomized trials indicate that periconceptional folic acid supplementation has a large effect on the recurrence of NTDs (70% reduction; 95% CI: 35–86). Four prevention-of-first-occurrence studies indicate a reduction in incidence of 62% (95% CI: 49–71). These two meta-analyses are the first to separate the effects of folic acid supplementation on NTD incidence from the effect on NTD recurrence.

In addition, there is increasing, although lower quality evidence regarding folic acid fortification of food. Our systematic review identified 10 before-and-after

Table 2 Quality assessment of trials of folic acid to prevent neonatal mortality from neural tube defects

No of studies (ref.)	Quality assessment					Summary of Findings				
				Directness		Intervention		Control		
	Design	Limitations	Consistency	Generalizability to population of interest	Generalizability to intervention of interest	Number NTDs	Number of births	Number NTDs	Number of births	Relative Risk (95% CI)
Neonatal mortality (NTD deaths):										
1[43]	Before and after	Low-quality population-based study	Not applicable	Only one study. Argentina	Yes	–	179 928		181 066	0.43 (0.27–0.67)[a]
Neonatal mortality (all cause):										
No studies identified										
NTD incidence										
4[14,33–35]	1 RCT 3 cohort		Consistent and all four studies showing benefit	all very different study sites	Folic acid supplementation studies	58	87 890	227	135 080	0.38 (0.29–0.51)[b]
8[31,32,41–46]	Before and after	low-quality population-based studies	Consistent and all studies showing benefit	All high- or middle- income countries	Yes. Folic acid fortification studies	915	1 124 946	2814	2 073 826	0.54 (0.46–0.63)[b]
Recurrent NTD incidence: low outcome-specific quality										
3[26–28]	RCT	Two unclear allocation	Consistent	addressing recurrence not primary incidence of NTDs	Yes	8	822	26	741	0.30 (0.14–0.65)[b]

[a]Directly calculated from study results.
[b]MH pooled RR.

Table 3 Estimated proportion of congenital abnormality deaths and numbers of neonatal deaths due to NTDs for 2005 by region (low-income/high neonatal mortality countries)

Region	Estimated total number of neonatal deaths due to congenital abnormalities/year[a] (uncertainty range)		Estimated number of neonatal deaths due to NTDs/year[b]	% of all neonatal deaths from congenital abnormalities that are attributed to NTDs
Asia				
Southeast	17 000	(10–40 000)	5000	29
Central	5000	(3–10 000)	1500	30
East	34 500	(9–135 000)	20 500	59
South	100 000	(26–270 000)	70 000	70
Asia total	156 500	(68–360 000)	97 000	62
N. Africa/ Middle East				
North Africa	9500	(4–21 000)	3000	32
Middle East	20 000	(12–37 000)	5500	28
N. Africa/ Middle East Total	29 500	(18–49 000)	8500	29
Sub-Saharan Africa				
West	34 500	(18 69 000)	8000	23
South	3000	(2–6000)	1000	33
East	30 000	(18–49 000)	6500	22
Central	12 000	(3–27 000)	2000	17
Sub-Saharan Africa Total	79 500	(55–122 000)	17 500	22
Other regions	41 000	(38–45 000)	8000	20
Total	306 500	(216–516 000)	131 000	43

[a]Provisional estimates for Child Health Epidemiology Reference Group for 193 countries using methods described previously.[48] Note that in high-mortality countries the input data is largely from Verbal Autopsy which under estimates congenital abnormalities, especially those without obvious external manifestations.
[b]Provisional estimates by the Child Health Epidemiology Reference Group for 193 countries based on systematic searches for prevalence data, and case-fatality rate data.

population-based studies of the effect of folic acid food fortification on the occurrence of NTDs. These large-scale studies consistently report substantial reductions in the incidence of NTDs or in perinatal or neonatal mortality due to NTDs. A meta-analysis of the eight included studies suggests that food fortification can reduce the incidence of NTDs by 46% (37–54%). This is the first meta-analysis that we are aware of for folic acid fortification and NTDs and shows a substantial and consistent effect even in large-scale programmes. Assuming that folic acid affects NTD occurrence but not severity or case-fatality rate, we assume that folic fortification will reduce NTD-specific neonatal mortality by 46%. There is emerging evidence that folic acid fortification reduces both the incidence and the severity of NTDs,[49–50] which would make this assumption conservative.

The effect of folic acid on incidence and mortality may be different in countries with higher baseline rate of NTDs, poorer diets (with higher levels of folate deficiency in women of child-bearing age) and without screening for, or termination of, affected pregnancies.

There is evidence of a complex dose–response relationship with different fortification regimes, depending on the initial average birth prevalence of NTDs and the additional intake of folic acid.[51] The estimate in this meta-analysis of folic acid-fortification effect is based primarily on white populations. A study from the USA reported lower background NTDs rates amongst black Americans compared to Hispanic or white groups, but also a reduced effect of folic acid fortification in the black American group.[52] In Australia, the 30% reduction in the incidence of NTDs seen following the introduction of the folic acid-supplementation recommendation and voluntary food fortification was limited to the white population, with no changes in the NTD rates amongst the aboriginal populations seen across this time period.[53] However, one large study in China

found very high rates of NTDs, which were substantially reduced by periconceptional folic acid.[34] Prevalence studies in South Asia report very high rates.[54–56]

We based our estimate on fortification rather than supplementation. Although efficacy studies of supplementation have shown a large potential biological impact, the widespread adoption of policies of folic supplementation in many high- and middle-income countries have generally produced disappointing results at a public health level. The barriers to supplementation are likely to be even greater in low-income countries and those with high levels of poverty and poor health-care infrastructure. However, maximizing effectiveness of fortification in low-income countries may also present challenges. What level of folic fortification should be adopted? What vehicle should be used? This is likely to be country/region specific, dependent on the proportion of the population who buy particular food staples, such as flour, maize or rice. Despite intense efforts, folic acid fortification may not reach the poorest, as was seen in Guatemala.[57]

The main limitation of this review and the resulting effect estimate is the lack of high-quality studies reporting the impact of folic acid supplementation or fortification on neonatal mortality. Our estimate for folic fortification is based on low-quality before-and-after population studies from Canada, the USA and three middle-income countries to determine the impact on incidence. Given the consistency of the effect size across studies, the quality can be upgraded to moderate, but once assumptions are applied to 'translate' this to mortality effect, the quality of the estimate is again downgraded to low. Further, possible sources of bias are that the review retrieved only published articles and that a single person was responsible for the screening and abstraction of the articles.

The proportion of neonatal deaths due to congenital abnormalities is problematic. Congenital abnormalities are under-reported in Verbal Autopsy and, indeed, also in hospital-based data since only obvious external abnormalities such as NTDs are detected yet the most common lethal congenital abnormalities are congenital heart disease, which are most likely to be misclassified as pneumonia. Hence the proportion of neonatal deaths attributed to congenital abnormalities is underestimated and reflects only those deaths due to clearly visible abnormalities. In addition, there may be systematic, selective misclassification of live-born babies with congenital abnormalities who die shortly after birth as stillbirths 'to protect the mother'. These global estimates (Table 3) are particularly uncertain for South Asia where both the prevalence of NTDs appears to be especially high, based on four studies, and yet the proportion of neonatal death attributed to congenital conditions is based on verbal autopsy and is low and very uncertain.[48]

The effects of folic acid on pregnancy outcome may extend beyond NTDs. Recent studies have suggested a possible effect on reducing spontaneous preterm delivery[58] and severe congenital heart disease.[59] Any benefit of universal folic acid food fortification on pregnancy outcome needs to be balanced against potential, but as yet unclear, adverse effects. There is very limited evidence that the amount of folic acid consumed from fortified foods has any adverse effects. Even in the USA amongst those who consume daily supplements with folic acid of 400 μg, the likelihood is low of exceeding a total intake of 1000 μg/day.[60–61] Very high serum folate levels, higher than those usually associated with fortification have been associated with potential adverse effects, but strong evidence of causation is lacking, e.g. masking of vitamin B12 deficiency amongst individuals with pernicious anaemia in the population and promoting progression of already existing pre-neoplasms.[62–65]

Conclusion

This review provides further evidence of the effectiveness of folic acid in reduction the incidence of NTDs. We estimate conservatively that folic acid fortification has the potential to prevent ~46% of NTD incidence and mortality, translating to ~13% of neonatal deaths due to visible congenital malformations. This estimate is slightly lower than the 57% reduction in NTD neonatal mortality reported following food fortification reported by one low-quality study in Argentina but lies within the 95% CI for that study (95% CI: 33–73).

A larger effect may be seen with folic acid supplementation, but the efficacy observed in supplementation trials has not been reproduced on a population level apart from in China, and this may not be transferable given the unique system of premarital health checks and a high percentage of planned pregnancies at the time of the study. The scaling up of food fortification in high- and middle-income countries has the potential to reach the majority of the population, although the practicalities of scaling up of food fortification in low-income countries with a high proportion of subsistence farmers have yet to be documented, and careful evaluation of the effects on NTD mortality and morbidity is also lacking. However, successful scaling up of folic acid fortification would lead to major reductions in the global burden of NTDs and morbidity reductions are likely to be of even greater public health significance than the mortality effects which are the focus of this review.

Supplementary Data

Supplementary data are available at *IJE* online.

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KEY MESSAGES

- ***Cause-specific mortality to act on*:** The proportion of congenital abnormality neonatal deaths that is due to neural tube defects (NTDs).
- ***Cause-specific effect and range*:** Food fortification with folic acid is estimated to lead to a 46% reduction in the incidence of and mortality from NTDs. Assuming NTDs to constitute cause for 29% of neonatal deaths due to visible congenital causes in low-income countries, folic acid food fortification may lead to a 13% reduction of visible neonatal congenital deaths.
- ***Quality of input evidence*:** Moderate quality (eight before-and-after population-based studies on incidence of NTDs, data consistent)
- ***Proximity of the data to cause-specific mortality effect*:** Low (effect on incidence) necessitating translation of the NTD-specific reduction to a reduction in neonatal deaths due to congenital abnormalities.
- ***Limitations of the evidence*:** The evidence may underestimate the effect on low-income populations based on comparison with one low-quality study reporting 57% reduction in neonatal mortality from NTDs. Most are incidence studies from middle/high-income countries, the outcome is distal to mortality and uncertain assumptions are applied to translate this to an estimated mortality effect. The data on mortality due to congenital abnormalities in low-income settings is limited and likely to reflect only obvious visible abnormalities.

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