

# Decline in the prevalence of neural tube defects following folic acid fortification and its cost-benefit in South Africa

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## ABSTRACT

**BACKGROUND:** In October 2003 South Africa embarked on a program of folic acid fortification of staple foods. We measured the change in prevalence of NTDs before and after fortification and assessed the cost benefit of this primary health care intervention. **METHODS:** Since the beginning of 2002 an ecological study was conducted among 12 public hospitals in four provinces of South Africa. NTDs as well as other birth defect rates were reported before and after fortification. Mortality data were also collected from two independent sources. **RESULTS:** This study shows a significant decline in the prevalence of NTDs following folic acid fortification in South Africa. A decline of 30.5% was observed, from 1.41 to 0.98 per 1,000 births (RR = 0.69; 95% CI: 0.49-0.98;  $p = .0379$ ). The cost benefit ratio in averting NTDs was 46 to 1. Spina bifida showed a significant decline of 41.6% compared to 10.9% for anencephaly. Additionally, oro-facial clefts showed no significant decline (5.7%). An independent perinatal mortality surveillance system also shows a significant decline (65.9%) in NTD perinatal deaths, and in NTD infant mortality (38.8%). **CONCLUSIONS:** The decrease in NTD rates postfortification is consistent with decreases observed in other countries that have fortified their food supplies. This is the first time this has been observed in a predominantly African population. The economic benefit flowing from the prevention of NTDs greatly exceeds the costs of implementing folic acid fortification.

## INTRODUCTION

NTDs are relatively common birth defects. The prefortification estimates of the prevalence vary in South Africa. In general, lower prevalences are found in urban regions such as Cape Town (1.3/1,000 births) (Buccimazza et al., [1994]), Pretoria (0.99/1,000 births) (Delpont et al., [1995]), and Johannesburg (1.18/1,000 births) (Kromberg et al., [1982]). Higher rates are reported in rural areas in the Limpopo Province (3.5/1,000 births) (Venter et al., [1995]), and an extremely high NTD prevalence has been found in rural Transkei districts in the Eastern Cape Province (6.1/1,000 births) (Ncayiyana, [1986]). An earlier mainly urban based surveillance system reported a prevalence of 1.2/1,000 births for the years 1994-2003 (International Clearinghouse for Birth Defects Surveillance and Research, [2005]). Christianson et al. ([2006]) gave an estimate for the country as a whole as 2.5/1,000 births.

Experimental and epidemiological evidence has shown that periconceptional dietary supplementation with folic acid can substantially decrease the prevalence of NTDs (MRC, [1991]; Ceizel et al., [1992]; Lumley et al., [2001]). In October 2003, South Africa embarked on a National Food Fortification Program to address micronutrient deficiencies in the population. The recommendations to do this had been published as long ago as 1978 (Metz et al., [1978]). Micronutrients added to staple foods such as maize meal and bread flour include: folic acid, vitamin A, thiamine, pyridoxine iron, and zinc. The Department of Health ([2003]) has set the level of fortification for folic acid in wheat flour at 1.5 mg/kg and in maize meal at 2.21 mg/kg. Maize meal and bread are among the most widely consumed

foods in South Africa. The milling industry is highly concentrated in South Africa, with 22 large-scale maize millers accounting for approximately 85% of all maize meal produced in the country. Seventeen mills produce about 95% of all bread and cake flour (Department of Agriculture, [2006]). These large millers independently test their products for the correct addition of micronutrients. A rapid rollout of fortified products accordingly took place, at approximately 90% coverage. The cost of fortification is borne by the industry.

The South African Department of Health designated four birth defects as priorities to be monitored: NTDs; cleft lip, cleft palate, or both; Down syndrome; and oculo-cutaneous albinism. The aim of this study was to establish baseline, prefortification prevalence rates and postfortification prevalence rates of NTDs and the three other priority birth defects (non-NTDs) among newborns to determine whether food fortification influences NTD prevalence.

## **METHODS**

Since the beginning of 2002 we have been conducting hospital based surveillance of NTDs (anencephaly, spina bifida, and encephalocele), cleft lip, cleft palate, or both, Down syndrome, and oculo-cutaneous albinism in various provinces of South Africa. In each sentinel site, appropriate health care workers received training in clinical recognition of the priority birth defects by a medical geneticist. Information on cases was extracted from hospital records and forwarded on a standardized notification form to the surveillance team. In this study 12 public hospitals in four provinces served as sentinel sites, as reporting from the other sites was inconsistent/incomplete for the entire study period. The participating sites reported the priority birth defects consistently at monthly periods both pre- and postfortification. NTD prevalence rates were established among live- and stillbirths during the period of prefortification (January 2003-June 2004) and the postfortification period (October 2004-June 2005). A 3 month intermediate period, July-September 2004, was excluded so that the pre and post phases could be clearly separated. The prefortification period included an allowance of 9 months for gestation following the introduction of fortification, such that none of these births could have been exposed to fortified foods in the periconceptional period. The denominator birth data during the study period averaged 53,000 births per annum. The birth population was in excess of 90% African.

Two additional independent sources of mortality data were also used to investigate changes in NTD rates.

### **Data Analysis**

Observed prevalence rates with 95% CIs were based on the Poisson distribution with normal approximation. Pre- and postfortification rates were compared using risk ratio (RR) analysis to measure the protective effect of folic acid fortification. We also calculated the ratio of the prevalence of NTDs to other priority birth defects in each time period. If reporting efficiency fell over the study period, then an observed drop in the prevalence rates of all defects would be in part an artifact, but we would expect the ratio of NTDs to the other defects to remain the same in the two time periods. The ratio is open to two possible biases: (a) that because it was known that there was an interest in NTDs and fortification, NTDs would be preferentially reported; and/or (b) that one or more of the other birth defects (such as oro-facial clefts) also had a reduction as a result of fortification. In either event the bias is conservative, leading to a lower reported decline than is actually the case.

## **RESULTS**

Table 1 shows a comparison of pre- and postfortification prevalence rates. There was a significant decline of 30.5% in the prevalence of NTDs, from 1.41 to 0.98 per 1,000 births (RR = 0.69; 95% CI: 0.49-0.98;  $p = .0379$ ), whereas the rates of the other birth defects combined did not change significantly (RR = 0.97; 95% CI: 0.69-1.36;  $p = .8460$ ). The ratio of NTDs to other non-NTD defects combined was 1.2 in the pre-, and 0.9 in the postfortification period, a 28.1% reduction.

<b>Table 1. Comparison of Pre- and Postfortification Rates of NTD and Non-NTD Birth Defects</b>						
<b>Province</b>	<b>Prefortification January 2003 to June 2004</b>			<b>Postfortification October 2004 to June 2005</b>		
	<b>NTD cases</b>	<b>Births</b>	<b>Rate/1,000</b>	<b>NTD cases</b>	<b>Births</b>	<b>Rate/1,000</b>
Eastern Cape	46	21,851	2.11	17	13,482	1.26
KwaZulu Natal	40	37,997	1.05	17	21,791	0.78
Mpumalanga	9	6,604	1.36	4	3,932	1.02
Free State	17	13,135	1.29	7	6,816	1.03
<b>Total</b>	<b>112</b>	<b>79,587</b>	<b>1.41</b>	<b>45</b>	<b>46,021</b>	<b>0.98</b>
			<b>95% CI:</b>			<b>95% CI:</b>
			<b>1.15-1.67</b>			<b>0.69-1.26</b>
<b>Province</b>	<b>Prefortification</b>			<b>Postfortification</b>		
	<b>Non-NTD</b>	<b>Births</b>	<b>Rate/1,000</b>	<b>Non-NTD</b>	<b>Births</b>	<b>Rate/1,000</b>
Eastern Cape	28	21,851	1.28	11	13,482	0.82
KwaZulu Natal	42	37,997	1.11	25	21,791	1.15
Mpumalanga	4	6,604	0.61	6	3,932	1.53
Free State	19	13,135	1.45	10	6,816	1.47
<b>Total</b>	<b>93</b>	<b>79,587</b>	<b>1.17</b>	<b>52</b>	<b>46,021</b>	<b>1.13</b>
			<b>95% CI:</b>			<b>95% CI:</b>
			<b>0.93-1.41</b>			<b>0.82-1.44</b>

Table 2 compares the pre- and postfortification rates of specific NTD conditions (anencephaly and spina bifida) and oro-facial clefts. Spina bifida shows the highest significant decline of 41.6% (RR = 0.58; 95% CI: 0.37-0.92;  $p = .0187$ ). The decline for anencephaly was only 10.9% (RR = 0.89; 95% CI: 0.50-1.60;  $p = .6985$ ). Oro-facial clefts showed a nonsignificant decline (5.7%) (RR = 0.94; 95% CI: 0.53-1.68;  $p = .8420$ ).

A linear relationship between prefortification NTD prevalence rates and the reduction in those rates following fortification was observed in Canada (De Wals et al., [2007]). A similar phenomenon was observed between provinces in this study ( $r^2 = 0.94$ ), with a regression coefficient consistent with the Canadian study.

**Table 2. Comparison of Pre- and Postfortification Rates of Specific NTDs (Anencephaly and Spina Bifida) and Oro-Facial Clefts**

Condition	Prefortification		Postfortification		Percentage decline
	Cases	Rate/1,000	Cases	Rate/1,000	RR (95% CI)
Anencephaly	33	0.41	17	0.37	10.9% RR = 0.89 (0.50-1.60)
Spina bifida	74	0.93	25	0.54	41.6% RR = 0.58 (0.37-0.92)
Oro-facial clefts	33	0.41	18	0.39	5.7% RR = 0.94 (0.53-1.68)

**Additional Evidence from Perinatal Mortality Surveillance**

In order to provide an independent data source and measure of the effect of folic acid fortification, an existing perinatal mortality surveillance system was also utilized, the Perinatal Problem Identification Programme (PIIP). Pattinson et al. ([2005]) aimed to identify the common causes of death and associated factors that could be addressed to reduce the perinatal mortality rate. Basic perinatal birth data and causes of death up to 7 days of age were recorded. A category of NTDs was included in the classification in anticipation of folic acid fortification. All perinatal deaths (stillbirths and neonatal deaths of 500 g or more) were recorded at 164 sentinel health care facilities spread throughout urban and rural areas of South Africa.

Table 3 shows a comparison of prefortification (2001-2003) and postfortification (2005-2006) perinatal mortality rates from NTDs. There was a significant decline of 65.9% in NTD perinatal mortality, from 0.42 to 0.14 per 1,000 births (RR = 0.34; 95% CI: 0.25-0.47;  $p < .001$ ). As a control, the perinatal mortality rate of hydrocephalus, unrelated to NTDs, did not change significantly (RR = 0.92; 95% CI: 0.54-1.57;  $p = .7732$ ).

**Table 3. Comparison of Pre- and Postfortification Perinatal Mortality Rates for NTDs and Hydrocephalus from the PIIP Surveillance System**

Perinatal condition	Prefortification 2001-2003		Postfortification 2005-2006		Percentage decline
	Deaths	Rate/1,000	Deaths	Rate/1,000	RR (95% CI)
NTD	204	0.419	46	0.143	65.9% RR = 0.34 (0.25-0.47)
Hydrocephalus	36	0.074	22	0.068	7.5% RR = 0.92 (0.54-1.57)

### Further Evidence from National Infant Mortality Statistics

It is also possible to detect a reduction in NTD mortality following fortification in national mortality statistics produced by Statistics South Africa ([2007]). Unit records of all registered deaths under 1 year of age for the period 1998 to 2005, coded to ICD-10 at the three character level, were analyzed annually. Because birth registration is incomplete, and the completeness of routine death registration is not precisely known and may vary from year to year, the proportion of NTDs to all other congenital anomalies was calculated, rather than an absolute rate. This data give us a longer prefortification baseline than the two sources of data presented earlier in this article (Fig 1). Between 1998 and 2003 there was no significant trend in the proportion of NTDs ( $\chi^2 = 1.36; p = .244$ ), while from 2003 to 2005 there was a strong downward trend ( $\chi^2 = 11.02; p < .001$ ). In 2003 the proportion was 12.37% (95% CI: 10.25-14.75) and in 2005 it was 7.57% (5.91-9.52). The decline of 38.8% in the proportion is significant ( $p = .0008$ ).

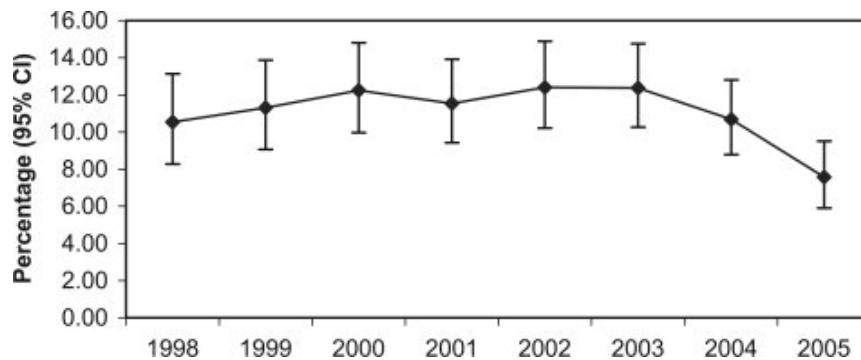


Figure 1. Proportion of NTD deaths to all other congenital anomalies, <1 year, South Africa 1998-2005.

### Population Cost Benefit of Folic Acid Fortification in South Africa

We estimated the cost benefit of fortification by comparing the direct cost of fortification against the direct cost of minimal medical intervention in the short term. The cost of folic acid at 2% of the fortification premix is R1.4 million (1 US\$  $\approx$  7 ZAR) per annum. In South Africa medical tariffs vary considerably amongst the public and private sector medical insurance companies, where 85% of the population do not have the benefits of private health insurance (Council for Medical Schemes, [2006]). The costing in this study was based on the Uniform Patient Fee Schedule Uniform Professional Fee Structure of the Department of Health ([2006]), which is used in provincial and government hospitals. Uniform Patient Fee Schedule Uniform Professional Fee Structure is considerably lower than private sector rates. It must be noted that although these procedures are listed, not all children born with these conditions will have the benefit of this quality of health care.

Table 4 shows the minimal medical interventions and estimated costs for appropriate care during the first year of life. Typically, as an example, the total cost for treatment in the first year of life for a newborn with myelomeningocele is about R70,000.

**Table 4. Estimated Costs of Treatment and Hospitalization during First Year**

Procedure	Cost
Closure of myelomeningocele	R10,300.00
Insertion of ventriculoperitoneal (VP) shunt	R11,683.00
Hospitalization (ward, intensive, and high care units)	R29,933.00
Laboratory tests and blood products	R2,500.00
Radiology	R5,675.00
Revision of clubfoot	R5,000.00
Minor procedures *	R5,000.00
<b>Total</b>	<b>R70,091.00</b>

\* Pediatric follow-up, urology in the form of catheterization, bowel washouts, and oral medication.

It is therefore not unreasonable to conservatively estimate the average cost of treatment of R100,000 per case during the first 3 years of life of a cohort. South Africa has a prefortification spina bifida rate of 0.93/1,000 and a birth population of 1.05 million. There are therefore approximately 976 cases of spina bifida per year. With a 41.6% reduction 406 cases are averted per annum, resulting in a saving of R40.6 million per annum. This gives a cost benefit ratio of approximately 30 to 1 for folate fortification as a cost effective primary health care intervention. If the true national prevalence rate for NTDs is greater than that observed in our hospital based surveillance system, the cost benefit ratio will be greater.

## DISCUSSION

This study has demonstrated a significant decline in the prevalence of NTDs following folic acid fortification in South Africa. This is the first time that data on the result of folate fortification have been presented for a predominantly African population. In addition to the main sentinel site surveillance, the PPIP surveillance system, an independent perinatal mortality data source, also shows a significant decline in perinatal deaths from NTDs, as did a third independent data set on cause specific infant mortality from national civil registration of deaths. All three systems showed a decline in NTD commencing at the time when fortification was introduced. In countries where it is not feasible to institute morbidity surveillance, national death registration (Setel et al., [2007]) or perinatal mortality surveillance may provide a suitable alternative.

The decrease in NTD rate postfortification is consistent with decreases observed in other countries that have fortified their food supplies. In Chile (Hertrampf et al., [2004]; Jorge, [2005]), Costa Rica (Chen et al., [2004]), Canada (De Wals et al., [2007]), and specifically Nova Scotia (Persad et al., [2002]), where mandatory fortification of basic foodstuffs has been implemented, more than 30% reduction in NTDs was noted. In the USA, the decline in spina bifida in association with fortification has been consistently greater than the decline in anencephaly (Mathews et al., [2002]; Williams et al., [2005]). A similar relative decline in spina bifida and anencephaly has been replicated in this study. There is no substantial prenatal intervention for NTDs in South Africa.

This study showed that Eastern Cape Province had the highest prefortification NTD rates and also had the highest decline of 40.1%. It is also noted that in a supplementation study in China there was a

greater decline in the north where rates were higher as compared to the south with its lower rates (Berry et al., [1999]).

This study also shows there was no significant reduction in oro-facial clefts, a decline of 5.7% being observed. Recent studies in Western Australia (Bower et al., [2006]) and in Canada (Ray et al., [2003]; Botto et al., [2006]) also showed no evidence of folate being an important factor in the prevention of birth defects other than NTDs.

An earlier mainly urban based surveillance reported annually to the International Clearinghouse for Birth Defects Surveillance and Research ([2005]) showed no significant trend for NTDs over the period 1994-2003, and infant mortality data also showed no trend for NTDs from 1998-2003.

The surveillance of NTDs, both before and after fortification, took place in an environment of one of the highest HIV infection rates in the world. The average HIV prevalence rate among pregnant women in South Africa was given by the Department of Health ([2005]) as 27.9% in 2003 and 29.5% in 2004, with an estimated 5 million individuals of both sexes infected with HIV (Dorrington et al., [2005]). Although some antiretroviral therapy (ARV) may increase the risk for NTDs (De Santis et al., [2002]), the rollout of ARV was slow (Stewart and Loveday, 2005), and by April 2005, only about 50,000 persons were on treatment with ARVs, so this is unlikely to have influenced the findings.

Although it is difficult to compare cost benefits of fortification in different countries, the cost benefit ratio in averting NTDs was approximately 30 to 1 in this study, in the United States 40 to 1 (Grosse et al., [2005]), and in Chile 10 to 1 (Llanos et al., [2006]).

## CONCLUSION

This study shows a significant decline in the prevalence of NTDs following folic acid fortification in South Africa. The decrease in NTD rates postfortification is consistent with decreases observed in other countries that have fortified their food supplies. This is the first time this has been observed in a predominantly African population. The economic benefit flowing from the prevention of NTDs greatly exceeds the costs of implementing folic acid fortification, as shown in other studies around the world, and is an extremely cost effective primary health care intervention.

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