



Integrated surveillance strategy to support the prevention of neural tube defects through food fortification with folic acid: the experience of Costa Rica

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Abstract

Purpose (1) To describe how Costa Rica implemented an integrated surveillance strategy of folate deficiency, neural tube defects (NTDs) prevalence, NTDs-associated infant mortality rate (NTDs-IMR), and folic acid food fortification (FAFF), to support with evidence NTDs prevention policies; (2) to disseminate updated data from monitoring programs.

Methods We performed a cross-sectional analysis, using the databases of national surveillance systems for NTDs outcomes to compare NTDs-prevalence and NTDs-IMR observed in the pre-fortification (1987–1998) and post-fortification (2010–2020) periods. In addition, using data from FAFF monitoring program (2010–2020), means of folic acid concentration (mg/kg) and folic acid daily intake ($\mu\text{g}/\text{day}$) were calculated for each fortified food (corn and wheat flour, rice and milk), as well as its contribution to folic acid estimated average requirement (EAR).

Results After FAFF Costa Rica showed a decrease of 84% in folic acid deficiency in women of childbearing age, as well as a 53% decrease in the prevalence of NTDs, falling from 11.82/10,000 to 5.52/10,000 livebirths. In addition, there was a 76% reduction in the NTDs-IMR from 77.01/100,000 to 18.66/100,000 livebirths. Between 2010 and 2020, all fortified foods provided an average contribution of 119% of the EAR of folic acid in the population.

Conclusion To reduce NTD risk, an integrated surveillance strategy is essential not only to base prevention strategies on evidence, but also to demonstrate their impact and improve interventions over time. The experience in Costa Rica provides evidence that this type of surveillance is feasible to be implemented in developing countries.

Keywords Folic acid food fortification · Neural tube defects · Surveillance · Developing countries

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Introduction

Neural tube defects (NTDs) are one of the leading causes of mortality, morbidity, and disability and a major preventable public health burden in many low- and middle-income countries (LMIC). The burden of NTDs around the world is high, with approximately 80% of reported prevalence estimates above 6.0/10,000 births, approximately 88,000 deaths per year, and 8.6 million disability-adjusted life years [1]. Highest prevalence is reported in LMIC [2] where NTDs may account for 29% of neonatal deaths due to observable birth defects [3].

In the Region of the Americas, median prevalence is estimated as 11.5 per 10,000 live births, ranging from 3.3 in Ecuador and Mexico to 27.9 in Guatemala [1]. Inside the Region of the Americas, Latin America reported prevalence varies greatly within each country and between countries,

influenced by methods of ascertainment, ranging from 2.6 per 10,000 (Rio de Janeiro, Brazil 2008) to 96.3 per 10,000 live births (Porto Alegre, Brazil 2009) [4].

There is sufficient evidence on the effectiveness of folic acid fortification of foods (FAFF) in the prevention of NTDs [5, 6]. Besides, FAFF has demonstrated to be cost effective even in LMIC countries [7].

The current global prevention proportion of FAFF preventable spina bifida and anencephaly cases worldwide is 23% of total potential prevention; thus, 215,027 FAFF-preventable cases occur each year; substandard or absent fortification policies are greatest in LMIC [8].

Costa Rica, a Central America middle-income country, implemented FAFF in 1997, with a large impact in raising blood folate levels in women of reproductive age [9] as well as in a sizeable reduction in NTDs-prevalence and NTDs-associated infant mortality (NTD-IMR) up to 2012 [10–12].

Excluding Venezuela, all Latin American countries have mandatory fortification legislation of wheat flour with folic acid, but few have established monitoring and evaluation components to assess the impact of NTDs prevention policies [4].

Public health surveillance includes the systematic and ongoing collection, analysis, and interpretation of health data, essential to the planning, implementation, and evaluation of practices, closely related to the timely dissemination to decision-makers, to implement public health programs [13]. No public health policy will be correctly implemented, evaluated, and improved without data provided by surveillance. However, several developing countries debate between spending their limited resources on the implementation of surveillance strategies and focusing these resources on interventions for NTDs prevention and care measures.

The objectives of this paper are as follows: to describe how Costa Rica has achieved an integrated surveillance strategy including multiple factors and events to implement, evaluate, and improve NTDs prevention strategies through food fortification with folic acid, and to disseminate the most current information on NTDs-prevalence, NTDs-IMR, and FAFF monitoring programs.

Methods

In Costa Rica, NTDs prevention policy through FAFF integrates various surveillance systems: the monitoring of folate deficiency in women of reproductive age; the monitoring of NTDs-prevalence and NTDs-IMR; the monitoring and verification of the food fortification with folic acid. This integrated surveillance has been proposed to accelerate NTDs prevention [14]. Based on published scientific articles, as well as current protocols, we describe how the different surveillance strategies began and evolved.

In addition, we performed a cross-sectional study using data about NTDs-prevalence and NTDs-IMR from the pre-fortification period (1987–1998), and the most recent post-fortification period (2010–2020).

Complementarily, using data from FAFF monitoring program (2010–2020), means of folic acid concentration (mg/kg) and folic acid daily intake ($\mu\text{g}/\text{day}$) were calculated for each fortified food (corn and wheat flour, rice and milk), as well as its contribution to folic acid estimated average requirement ($\text{EAR} = 400 \mu\text{g}/\text{day}$) [15].

Data were obtained from the national surveillance systems: (1) the Costa Rican Birth Defects Register Center (CREC, acronym in Spanish), (2) the National Institute of Statistics and Censuses (INEC, acronym in Spanish) which has an online query for infant deaths by cause, and (3) the National Reference Center of Bromatology (CNRBro, acronym in Spanish) that leads monitoring program of FAFF. CREC and CNRBro are part of the Costa Rican Institute for Research and Teaching in Nutrition and Health (INCIENSA, acronym in Spanish), which is a public institute dependent from the Ministry of Health (MH). The Research Directorate of INCIENSA and Directorate for the Regulation of Products of Sanitary Interest of the MH, approved the use of aggregated data derived from surveillance systems to make this manuscript.

Blood folate monitoring

Costa Rica monitors the level of blood folate in the population through National Nutrition Surveys (NNS) since 1996 and approximately every 10 years. For the 1996 NNS, serum folate concentrations were determined using solid phase radioimmunoassay [16]; for the 2008–2009 NNS [9], a liquid phase competitive chemiluminescent enzyme immunoassay was used. These surveys calculated both the median serum folate and the percentage of the population with blood folate deficiency ($\leq 6 \text{ ng/ml}$). Given that the laboratory techniques were different in each survey, we will present only the percentage of women of reproductive age with serum folate levels considered deficient.

Although in Costa Rica the NNS are meant to be carried out every 10 years, the 2019 NNS was not implemented due to limited financial resources, aggravated by the COVID-19 pandemic.

NTDs-prevalence and NTDs-associated infant mortality

In Costa Rica, mandatory birth defects surveillance—including NTDs—began in 1985 [17] with the creation of the CREC, including all death or live births of more than 500 g of weight and more than 20 weeks of gestational age. Nevertheless, the data on stillbirths is of questionable quality, since many hospitals in the network do not report these data. In 2008, the reporting age increased from hospital discharge to the first year of

life [18]. CREC has a central coordinating group, integrated by two pediatrician-epidemiologists and one secretary. This group coordinates a network of 32 hospitals (28 public and 4 private-hospitals), which covers over 98% of all national livebirths. The National Children Hospital (NCH)—the country's only national referral center for birth defects—became a member of CREC since 2008, together with secondary pediatric health centers with pediatric services. The Birth Defect Surveillance Protocol [19] guides the network procedures.

CREC is member of several international networks such as International Clearinghouse of Birth Defects Surveillance and Research, and the Latin American Registry of Congenital Malformations [20].

The surveillance system was intended to be simple, flexible, feasible, and inexpensive. Its implementation required a mix of political will, capacity building in the form of technical support to provide theoretical and practical capacities, and leadership of several people committed to children's health, selected in each maternity to motivate and convince their peers of the relevance of the registry.

As part of its strategy, CREC monitors infant mortality due to congenital defects. Since 2016, CREC included all local infant mortality commissions in the country, and they became great allies of the network.

For this analysis, prevalence data were updated by cross-checking the data reported to CREC with the mortality data from INEC. For congenital anencephaly and encephalocele defects, we found that for several years, infant mortality cases exceeded the cases reported to CREC. Thus, the highest number of cases reported between mortality and cases reported to CREC was considered prevalent cases.

We calculated temporal trends of NTDs-prevalence and NTDs-IMR with a 95% confidence interval (95% CI) for all NTDs from 1987 to 2020. Then, we compared all estimates between post- and pre-fortification periods by estimating prevalence ratios (PR) and infant mortality ratios by specific defect (anencephaly, encephalocele, and spina bifida), and the percentages of decrease for every estimated.

Pre-fortification period (1987–1998) does not include data from 1992 to 1995, because during this period only 8 out of more than 20 hospitals participating in CREC were reporting, so NTDs-prevalence was grossly underreported in these years. Besides, pre-FAFF period includes 1998 data, because mandatory FAFF was implemented in October 1997; thus, the potential effect in NTDs-prevalence was not expected until the end of 1998.

Folic acid levels in fortified foods

Systematic implementation of the verification of compliance with the fortification standards began after FAFF implementation (1997). Monitoring is done by laboratory analysis of fortified food samples. In a staggered manner, the chemical

analyses of the different micronutrients were incorporated according to the type of food-vehicle. CNRBro and the MH carry out this work jointly: the latter provides financial resources, while the former is the technical partner. Every year a sampling plan is defined, the MH collects the samples, and CNRBro performs the laboratory tests and sends the results to the MH. Then, MH evaluates the results contrasting with the official fortification standards (defined by executive decrees); if non-compliance is detected, a health order is sent to the food manufacturer for appropriate action.

The Costa Rican fortification program uses different technologies according to the food vehicle to be fortified. In the case of rice, it uses head rice enrichment strategy [21, 22] through extrusion and rinse-resistant coating technologies [23]. For the flours (wheat and corn), the fortification process takes place directly in the mills, and for milk the fortification occurs before pasteurization and homogenization process. In all cases, the stage of premix fortification is carefully selected to guarantee the maximum homogenization in the final product.

To present results of FAFF monitoring program for the post-fortification period (2010–2020), we calculated the mean of fortification with folic acid (FFA, milligrams of folic acid per kilogram of food) by food and year, and the mean of folic acid daily intake (FADI, μg of folic acid contributed by individual food per day). Besides, according to the reported consumption of rice, milk, corn, and wheat flour in the 2008–2009 NNS and based on the fortification values established by decree, the percentage reached of target folic acid EAR ($400 \mu\text{g}/\text{day} = 100\%$) [15] was calculated. Using the means of each fortified food per year, the contribution to the percent of EAR of folic acid per year and per food was calculated.

Results

Before FAFF in 1997, four NNS had been carried out (1966, 1975, 1979, and 1982) that showed changes in the nutritional status of the population [24]. Nutritional anemia was identified as a public health problem in Costa Rica before 1996 NNS, primarily due to iron deficiency and to a lesser extent to folate deficiency [16]. On the other hand, CREC showed a high prevalence of NTDs in 1996 (12.22 per 10,000 livebirths, 95% IC: 9.79–14.65). This scenario prompted the health authorities to include the measurement of serum folates in the population in the 1996 NNS.

By this time, the country already had a positive experience with large-scale food fortification, including fortification of salt with iodine and of sugar with vitamin A [25]. With this background, and to address the high prevalence of NTDs, the health authorities decided to implement the FAFF strategy. In 1997, the wheat flour's fortification decree (initially proposed in 1958) was modified to add folic acid

[26]. Over the following years, other foods were gradually included in the list of foods fortified with folic acid: corn flour in 1999 [27], milk in 2001 [28], and rice in 2002 (the decree was published in december 2021) [29].

Currently in Costa Rica, the FAFF strategy includes four food vehicles: rice, milk, corn, and wheat flour. Selection of these foods was based on the consumption habits of the population (obtained in NNS) and accessibility of these foods to the population (price). The fortification levels were established by executive decrees, considering a coverage of 100% of the EAR (400 µg/day). Figure 1 summarizes the timetable for the implementation of food fortification programs, serum folate monitoring, and neural tube defects surveillance in Costa Rica.

Monitoring of blood folate concentration in women in reproductive age

In the 1996 NNS, the prevalence of folate deficiency (< 6 ng/ml) in women of childbearing age was 24.7%, 4% with severe deficiency (< 3 ng/ml), and 20.7% with moderate deficiency (3–5.99 ng/ml) [16]. At that time, there were no resources to measure erythrocyte folate. In the 2008–2009 NNS [9], 10 years after the implementation

of mandatory FAFF, the prevalence of folate deficiency in women of childbearing age was 3.8% (measurement of erythrocyte folate was not implemented at that time), showing a 84% reduction compared to the 1996 NNS. This reduction was 78% in the Greater Metropolitan Area (the country’s most developed area) and was greater in rural areas, with 97% of reduction.

Prevalence of NTDs

There has been a significant reduction in NTDs-prevalence from 1987 to 2020, with a significant drop after FAFF (Fig. 2). There was also a significant reduction in NTDs-prevalence for each type of defect, being greater for encephalocele, followed by anencephaly and spine bifida (Table 1).

Infant mortality attributable to NTDs

Infant mortality from NTDs fell significantly throughout the 1987–2020 study period. Even though the IMR trend for NTDs had a downward trend, the reduction increased significantly after FAFF (Fig. 3). The proportion of

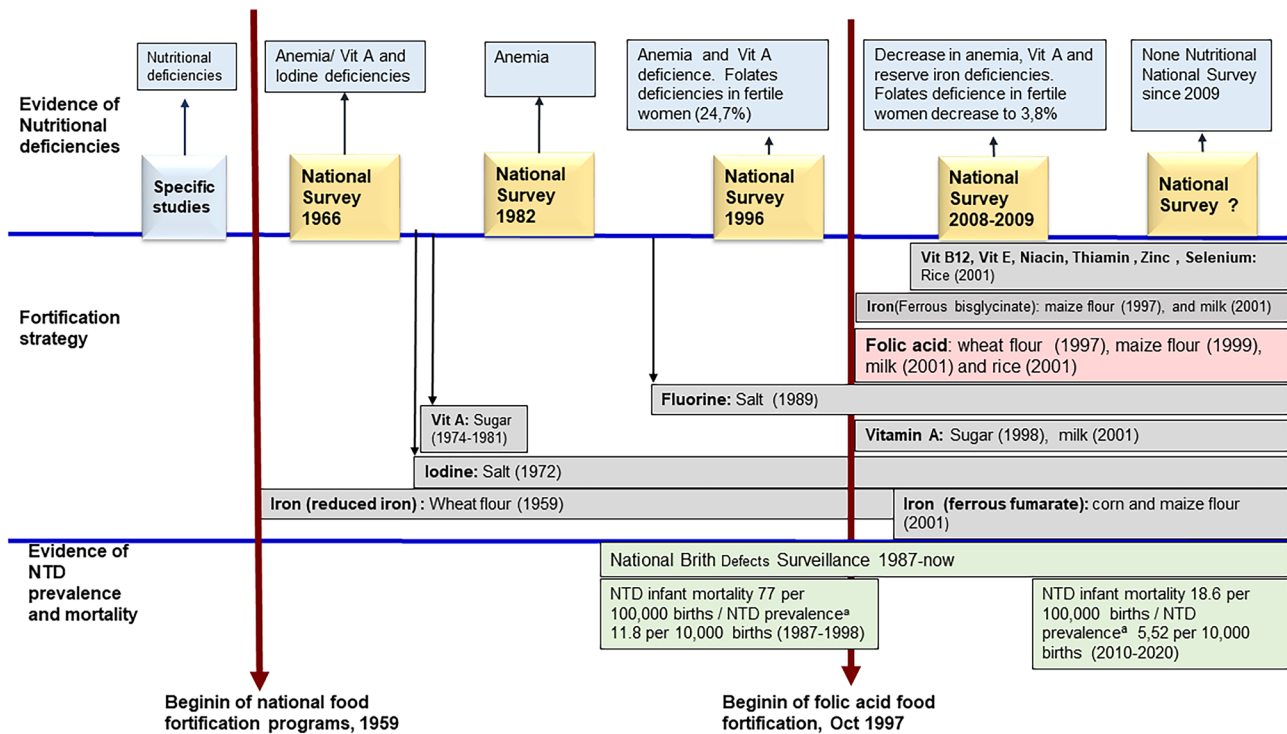


Fig. 1 Timetable describing the food fortification programs, serum folates monitoring, and neural tube defects surveillance as part of the integrated strategy of NTDs prevention in Costa Rica. ^aPrefortification period (1987–1997) does not include data from 1992 to 1995 (gray dots in the prevalence line) because only 8 from more than 20 hospitals participating in CREC were reporting and coverage showed a significant decrease. Prevalence of neural tube defects was updated

for each period by crossing over data bases of CREC (prevalence) and INEC (mortality. Source: Nutritional deficiencies were documented from National Nutrition Survey 1996 [16] and 2008–2009 [9]; fortification strategy was included in Executive Decrees [26–29]. Data for NTD mortality provided by INEC 2022, and data on NTD prevalence were available from CREC, 2022

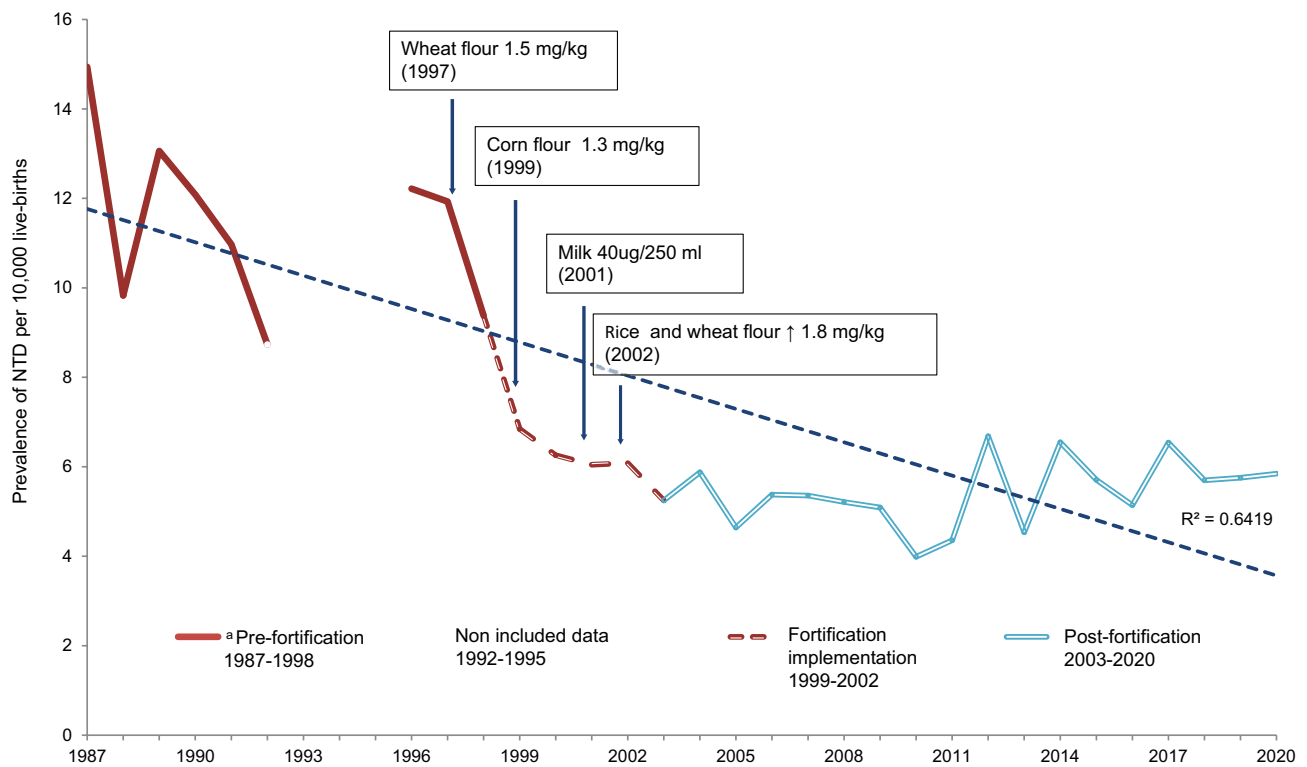


Fig. 2 Prevalence trend for neural tube defects per 10,000 live-births in Costa Rica 1987–2020. ^aPrefortification period (1987–1998) does not include data from 1992 to 1995 (space without data in the prevalence line) because only 8 from more than 20 hospitals participating

in CREC were reporting and coverage showed a significant decrease. Prevalence of neural tube defects was updated for each period by crossing over databases of CREC (NTD-prevalence) and INEC (NTD-infant mortality). Source: CREC-INCIENSA Costa Rica 2022, INEC 2022

NTDs within general infant mortality fell 60%, from 5.50% in the pre-fortification period, to 2.23% in the post-fortification period. Similarly, the proportion of

NTD within IMR by birth defects decreased by 68% between the pre- and post-fortification periods, going from 19.20% to 6.33% (Table 2).

Table 1 Changes in prevalence of neural tube defects (NTDs) comparing pre-fortification period and post-fortification periods. Costa Rica 1987–2020

Period/NTD type	NTD prevalence per 10,000 live births (95% CI) ^a	Prevalence ratio (prefortification referent)	Decrease relative to prefortification prevalence (%)
Pre-fortification^b (1987–1998)			
Anencephaly	3.05 (2.62–3.48)	-	-
Encephalocele	2.71 (2.31–3.11)	-	-
Spina bifida	6.06 (5.45–6.66)	-	-
Total NTDs	11.82 (10.98–12.66)	-	-
Post-fortification (2010–2020)			
Anencephaly	1.54 (1.26–1.82)	0.50	50%
Encephalocele	0.67 (0.49–0.85)	0.25	75%
Spina bifida	3.31 (2.90–3.72)	0.55	45%
Total NTDs	5.52 (4.99–6.05)	0.47	53%

^aPrevalence of neural tube defects was updated for each period by crossing over data bases of CREC (prevalence) and INEC (mortality)

^bPrefortification period (1987–1997) does not include data from 1992 to 1995 because only 8 from more than 20 hospitals participating in CREC were reporting and coverage showed a significant decrease

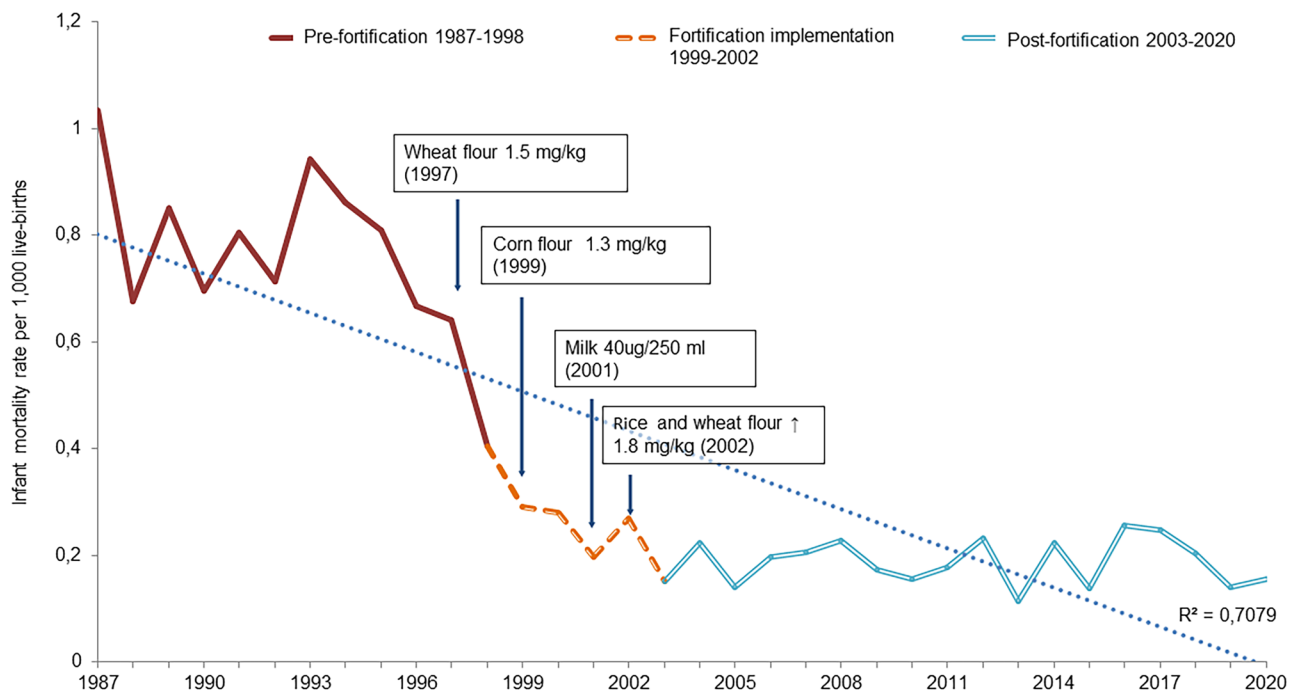


Fig. 3 Infant mortality rate from neural tube defects before and after folic acid food fortification, Costa Rica 1987–2020. Source: data from Costa Rican National Institute of Statistics and Census (INEC), January 2022

Folic acid in fortified foods

The selection of the number of fortified food samples included in this work is variable since it is based on two assumptions: first, by law, any food sold in the Costa Rican market must be fortified; second the fortification process (addition of the pre-mix to the vehicle feed) is homogeneous. The latter is based on the homogeneity evaluation of a large number of food samples at the beginning of the fortification program.

Due to their physical characteristics (liquid and powdered, respectively), milk and flour are foods that allow for

a very uniform distribution of the fortifier. In rice, both the food and the fortifier (extruded rice grain or rinse-resistant coating technologies) have granulometry similar to each other and higher than the flours, so there is greater difficulty in homogenizing the fortification processes and therefore greater variability in the contents of folic acid. Figure 4 shows how the interquartile distance q_2-q_3 (represented by boxes) of the three foods widen as their granulometry increases when going from wheat to rice.

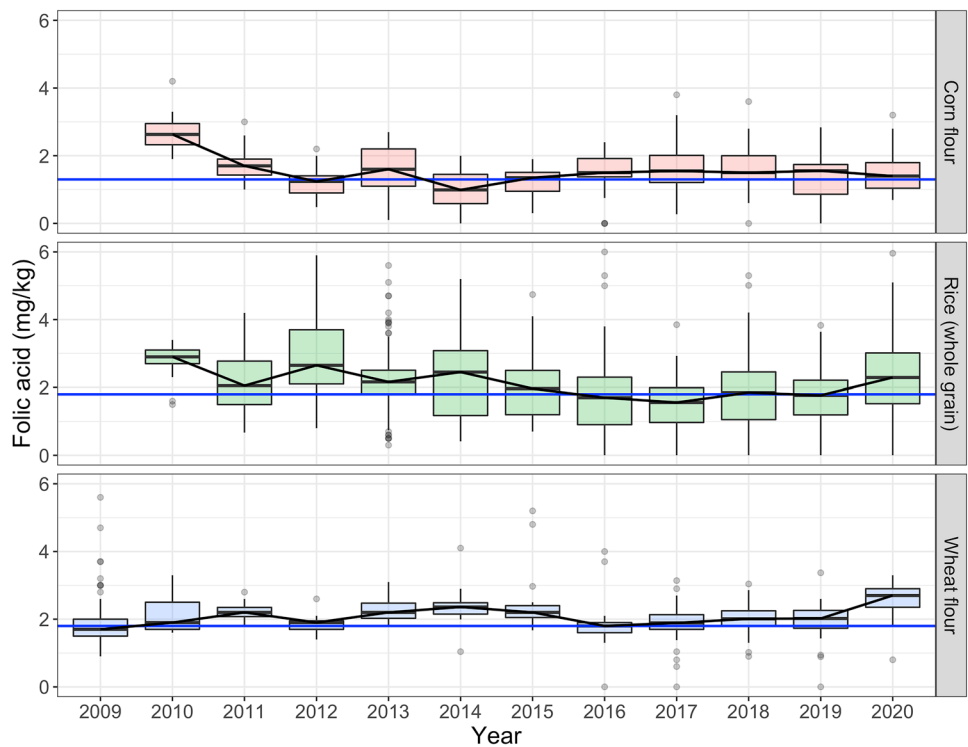
Another aspect that influences this variability is related to the fortification process directly in the mills. The flours

Table 2 Changes in infant mortality rate from neural tube defects (NTDs-IMR) by pre-fortification period and post-fortification periods. Costa Rica 1987–2020

Period/NTD type	NTDs-IMR per 100,000 live births (CI95%)	NTDs-IMR ratio (prefortification referent)	Decrease relative to prefortification (%)
Pre-fortification (1987–1998)			
Anencephaly	27.37 (27.28–27.46)	-	-
Encephalocele	29.87 (29.78–29.96)	-	-
Spina bifida	19.77 (19.69–19.85)	-	-
Total NTDs	77.01 (76.93–77.10)	-	-
Post-fortification (2010–2020)			
Anencephaly	15.25 (15.17–15.33)	0.56	44%
Encephalocele	2.50 (2.46–2.53)	0.08	92%
Spina bifida	0.92 (0.90–0.94)	0.05	95%
Total NTDs	18.66 (18.58–18.75)	0.24	76%

Source: data from Costa Rican National Institute of Statistics and Census (INEC), January 2022

Fig. 4 Folic acid content in cereals fortified by decree in Costa Rica, 2010–2020. Standard values in the blue line: in wheat flour 1.8 mg/kg [26], in corn flour 1.3 mg/kg [27], in rice 1.8 mg/kg [29]



are fortified during milling, which guarantees an appropriate distribution of the additives as well as the added nutrients, while in rice, the fortifier is added before packaging and mixing technologies could not guarantee homogenization as in flours.

Figure 5 shows the content of folic acid from milk; the levels found are above the fortification standard and show a greater dispersion than in fortified cereals. This could be due to the different types of milk consumed in the country (whole, low fat and skim milk).

Fig. 5 Folic acid content in fortified milk by decree in Costa Rica, 2010–2020. Standard values in blue line: milk 4.0 µg/250 ml [28]

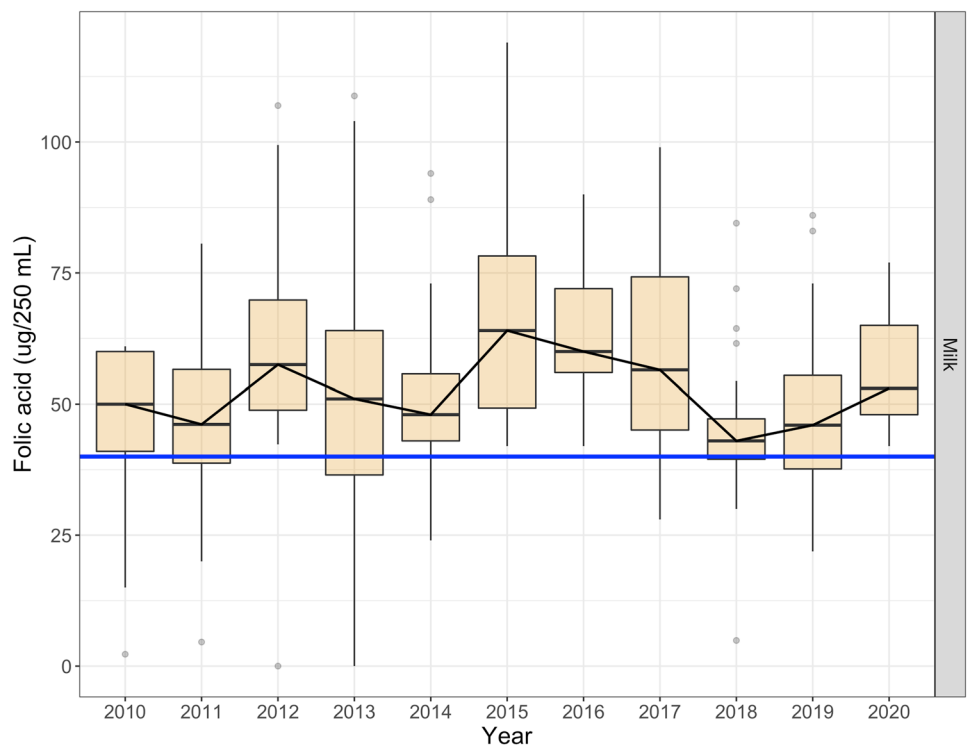


Table 3 Variation of the contribution of folic acid to the diet according to food fortified with folic acid per year in Costa Rica 2010–2020

Food	Daily grams fortified food consumed (g/capita/day) ^a	FFA ^b , FADI ^c and % of EAR ^d calculated in fortified food samples	Levels	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Rice	120	Mean of FFA (mg/kg) ^e Mean of FADI (µg/day) % of EAR N	1.8 216 54 -	2.9 348 87 20	2.1 246 62 74	2.7 318 80 252	2.2 259 65 208	2.5 294 74 36	2.0 235 59 38	1.7 204 51 95	1.6 187 47 117	1.9 222 56 139	1.8 212 53 103	2.3 275 69 59
Corn flour	15	Mean of FFA (mg/kg) ^e Mean of FADI (µg/day) % of EAR N	1.3 20 5 -	2.6 39 10 10	1.7 26 6 29	1.2 19 5 24	1.6 24 6 17	1.0 15 4 19	1.4 20 5 20	1.5 23 6 28	1.6 23 6 37	1.5 23 6 61	1.6 23 6 24	1.4 21 5 27
Wheat flour	48	Mean of FFA (mg/kg) ^e Mean of FADI (µg/day) % of EAR N	1.8 104 26 -	1.9 110 28 5	2.2 128 32 24	1.9 110 28 11	2.2 128 32 14	2.4 137 34 11	2.2 128 32 19	1.8 104 26 25	1.9 110 27 32	2.0 117 29 34	2.0 117 29 26	2.7 157 39 10
Milk	145	Mean of FFA (mg/kg) ^e Mean of FADI (µg/day) % of EAR N	0.4 58 15 -	0.50 73 18 9	0.46 67 17 14	0.58 83 21 30	0.51 74 18 35	0.48 70 17 28	0.64 93 23 30	0.60 87 22 17	0.57 82 20 48	0.43 62 16 43	0.46 67 17 32	0.53 77 19 17
All fortified foods		% of EAR total	99	143	117	133	121	129	119	104	100	106	105	132

^aFood consumption was obtained from the consumption results of the National Survey of Nutrition 2008–2009; apparent consumption was the methodology used because it allows a quick and minimally invasive calculation; it is important to highlight that it could lead to an overestimation. For the flours, both the quantities of flour itself and the contributions of flour from the different products derived from them were taken. For milk, all types consumed were included, including powdered milk; in the latter, its reconstitution was calculated according to the type of milk

^bFortification with folic (FFA) is the level of milligrams of folic acid per each kilogram of food

^cFolic acid daily intake (FADI) is the content of folic acid (µg) contributed per day from each food

^d% of estimated average requirement (% of EAR) is the contribution of each fortified food to the total EAR (estimated average requirement = 400 µg/day)

^eThe means exclude outliers (atypical data)

According to mandatory standards, the percentage of the target folic acid EAR ($400 \mu\text{g} / \text{day} = 100\%$) reached was 99%. Table 3 shows how the fortification with folic acid per food (expressed in mg/kg) is mostly above the minimum value established by decree. The percentage of EAR reached per year, taking into consideration all fortified foods, showed an average of 119% for the 2010–2020 period. This shows that the program has been efficient during the time contemplated in this study.

Discussion

Increasing the blood folate concentration in women of childbearing age has demonstrated to be effective in primary and secondary prevention of NTDs [8, 30, 31]. There are several approaches to improve folate status, including improving folate intake through dietary diversification, supplementation, and food fortification. In practice, it may be difficult to obtain the target 400 mcg/day of folate recommended to prevent NTDs from diet. Supplementation faces many challenges as public health intervention, including that more than half the pregnancies on a global level are not planned [32], which makes it more challenging to consume the required supplements before conception. Therefore, large-scale FAFF has emerged as the most cost-effective intervention to improve folate status at the population level [7, 33]. Currently, about 80 countries have mandatory FAFF programs [34], but few have monitored their effectiveness establishing proper quality assurance monitoring and evaluation practices, and even fewer have established appropriate NTDs surveillance systems or correlated these with folate determinations, both at the biological level and in the fortified foods.

We recognize that in countries with limited resources FAFF can represent a big challenge due to the complex dynamism involving different factors: although the government is responsible for setting the fortification standards, fortification activities are ultimately in charge of the food industry (which assumes the cost of the fortificant and complying with the correct addition of the premix); changing consumption habits in the population as well as particular habits in specific segments of it that may limit their access to fortified foods; and underlying conditions that may impact consumer's decision to eat the fortified foods. However, the Costa Rican experience presented on this paper shows how a multi-pronged approach to monitor and evaluate the effectiveness of FAFF can be successfully implemented.

Based on the results of successive NNS, the Costa Rica government became aware of the low level of folate intake by the population. This evidence was further reinforced by acknowledging a high prevalence of NTDs evidenced by the birth defects national surveillance system including reported

cases, discharge databases, and mortality registries, following established, uniform protocols. The choice of staple foods selected for large-scale FAFF was done on a step-wise fashion, taking into consideration consumption habits, availability, and price. As more foods were included in the fortification program, the levels of fortification for each of them were adjusted, both to comply with the recommended level of intake as well as to not exceed the upper tolerable limit of folate. Continued surveillance of blood folate levels has shown an increase in the population comparing pre- with post-fortification periods, and both NTDs surveillance and NTDs-IMR have responded in a way consistent with the improvement of the folate status in the population. Similar responses have been found in other countries, including Australia [35], Chile [36], and Canada [37].

Data from different countries around the world has shown that with well-established mandatory large-scale FAFF programs, the prevalence of NTD can be brought down to a minimum of $5\text{--}6 \times 10,000$ births [1, 2, 8, 30]. As shown in previous publications [11, 12], and confirmed with our more recent information, this has also been the case in Costa Rica, where the prevalence of NTDs changed from $11.8 \times 10,000$ livebirths pre-fortification to $5.5 \times 10,000$ post-fortification. Furthermore, NTDs-IMR also showed a substantial decline, from $77.01 \times 100,000$ livebirths to $18.66 \times 100,000$. Our data also showed that, although in Costa Rica infant mortality for all causes and infant mortality for congenital defects have decreased significantly in recent decades [38, 39], the significant and sustained fall in NTD-IMR is mostly consequence of the decrease in the prevalence of serious defects such as anencephaly (50% reduction) and encephalocele (75% reduction), in addition to the reduction in the most common NTD, spina bifida (45% reduction).

Although the WHO recommends an intake of $400 \mu\text{g/day}$ of folic acid to protect against the risk of folate-responsive NTD, recent data modelling the proportion of folate-preventable spine bifida and anencephaly supports that a minimum daily intake of 200 mcg of folic acid may be sufficient to provide high protection [8]. In support of this lower level of intake providing protection against NTDs, our data showed that the steepest decline on these birth defects occurred in the first 3 years post-FAFF (Figs. 4 and 5), when only one staple food (wheat flour) was being fortified. As other foods were included in the policy, subsequent declines were observed in the population, likely showing that larger segments of the population were receiving the benefit of the program. Monitoring the amount of folic acid present in the staple foods fortified in Costa Rica (wheat, corn, rice, and milk), our analysis showed that even if specific segments of the population consumed the four foods (Table 3), their intake would be $572 \mu\text{g/day}$, slightly above the EAR but way below the UTL of $1000 \mu\text{g/day}$ [40].

Therefore, according to our results, the strategy of fortifying several foods with folic acid has been successful insofar

as it is complementary (several foods) and universal (all options in the market for the same food). The underlying assumption is that the daily intake of folic acid will not be achieved by most of the population with consumption of one single fortified food, but it may be achieved with several. Furthermore, these data also point out that starting a fortification program, even when the fortified food does not reach the whole population, will provide tangible benefits in reducing the risk of NTDs; and that the inclusion of other fortified staples will help expand this benefit. This strategy has come to resolve the heterogeneity of the population's consumption habits, and has given responsibility for population health to various food industry players, creating an awareness of shared responsibility to contribute to public health, and reducing the resistance of producers to assume the cost and effort of fortification. The social commitment and the will of the food industry to continue with the FAFF program has been key in Costa Rica. The data collected from the different sources of information have served as a basis to create an integrated surveillance system, and this has been instrumental to increase awareness among these private actors and to show them that this strategy works.

Following the fact that our evaluation was not planned at the outset of the activities described, our study faced several limitations. The laboratory techniques used to measure blood folate status have shown changes over time, so results may not be strictly comparable. Data collection has shown some lapses over time, including underreporting of NTDs-prevalence between 1992 and 1995, as well as the absence of a NNS in 2019, due to limited financial resources and constraints imposed by COVID-19 pandemic. We acknowledge that the recommended indicator to evaluate the adequacy of folate status in providing the largest protection for NTDs is derived from measurement of red blood cell folate [41], which has not been determined in Costa Rican population. However, blood folate is a good indicator of recent ingestion of folic acid, and as such, is acceptable to be used at a population level to reflect changes in folate intake [42]. We recognize that these cross-sectional analyses do not conform to the widely accepted criterion of a randomized control trial to support causality, but the evidence provided through this comprehensive analysis conforms to several of Hill's criteria to derive causality, as it shows evidence of biological coherence, plausibility, and temporality [43]. Observational studies coming from surveillance systems provide the evidence needed in public health due to lack of feasibility and other inherent limitations of randomized controlled trials. In implementing evidence-based policies, an important but often overlooked consideration is the likelihood of harm from not assuming causality and thus making no change in current policy [6].

A recent study revealed that the presence of a registry or surveillance program for NTDs increases with country income level; likewise, the risk of bias of the reported prevalence increases as the income level of the countries decreases [1]. Lack of population-based surveillance contributes to gaps in our knowledge of NTDs in developing world; thus, funding for birth defects surveillance is urgently required to plan and develop a functional primary prevention infrastructure for future births; over time, the health and economic returns would be significant [44].

We have shown that the collection of solid evidence to guide decisions in public health is a sound approach leading to the improvement of the health status of the population. Large-scale food fortification has been recognized as one of the most effective and cost-efficient public health interventions [45, 46]. An integrated surveillance strategy is essential not only to base prevention strategies on evidence, but also to demonstrate their impact and improve interventions over time. The experience in Costa Rica provides evidence that this type of surveillance is feasible in developing countries.

Author contribution All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed mainly by Adriana Benavides and Oscar Fernández with the help of Maria de la Paz Barboza and Thelma Alfaro. The first draft of the manuscript was written by Adriana Benavides and edited by Homero Martínez; all authors reviewed and commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability The data that support the findings came from different sources:

Data of NTD infant mortality of this study are available without restrictions, in aggregate and anonymous form, from National Institute of Statistics and Census (www.inec.go.cr): the data on deaths in children under 1 year of age are available in the online consultation system, while the data on neonatal deaths are available at request. Pooled anonymous data of NTD prevalence from Centro de Registro de Enfermedades Congénitas (CREC), are available from the corresponding author on reasonable request with the permission of the Directorate of Research of INCIENSA. Data of monitoring of food fortification are available from the corresponding author on reasonable request with the permission of the CNRBro of INCIENSA, Directorate of Research of INCIENSA and Directorate for the Regulation of Products of Sanitary Interest of the MH.

Declarations

Ethics approval The use of aggregated data derived from surveillance systems was approved by the Research Directorate of INCIENSA and Directorate for the Regulation of Products of Sanitary Interest of the MH.

Consent for publication As this study utilized pooled, non-identifiable data collected from surveillance systems, it was excluded from the Research Ethics Committee review and the requirement of informed consent.

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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