

Fortifying Flour with Folic Acid to Prevent Neural Tube Birth Defects

Opportunity

Fortifying flour with folic acid is an effective way to reduce the occurrence of neural tube defects (NTDs) at a national level⁴.

The majority of NTDs can be prevented with the consumption of 400 micrograms of folic acid daily before conception and during early pregnancy⁷.

What are Neural Tube Defects?

After conception, a neural tube forms within 28 days and develops into the brain and spine¹. Birth defects occur when the neural tube fails to close properly. This can result in neural tissue being exposed and susceptible to damage¹.

The most common neural tube defects (NTDs) are spina bifida, which can lead to permanent disability, and anencephaly which always causes death². An estimated 320,000 newborns are affected by NTDs each year worldwide³.

Why Fortify Flour with Folic Acid?

Most NTDs can be prevented with adequate folic acid intake^{4,5,6}. The World Health Organization (WHO) recommends that women consume 400 micrograms of folic acid daily, starting from two months before a planned pregnancy through 12 weeks of gestation, to prevent NTDs⁷.

Taking folic acid supplements reduces the risk of NTDs⁸. However, taking daily supplements requires behavioral change. A review of 49 studies in 22 countries reported that folic acid supplement use was low and inconsistent (ranging from 0.5% in Italy to 52% in the Netherlands)⁹. Moreover, approximately half of all pregnancies worldwide are unplanned; women who are not planning a pregnancy may not take supplements during the periconceptional period¹⁰.

Mandatory programs to fortify flour with folic acid have been implemented in at least 80 countries¹¹. Fortification does not require consumer behavior change, and it improves the folate status of women of childbearing age—before they get pregnant¹². Increasing levels of folic acid in staple foods through fortification increases the likelihood that women will receive adequate amounts of folic acid needed to prevent NTDs¹³.

Effectiveness of Fortifying with Folic Acid

A total of 36 studies that compared the prevalence of NTDs before and after large-scale folic acid fortification programs in 13 countries were reviewed (Figure). In these countries, between 1 and 3 milligrams of folic acid were added to each kilogram of wheat flour alone or in combination with maize flour. The prevalence of NTDs before fortification ranged from 3.8 to 43.7 per 10,000 births, which became less variable after flour was fortified with folic acid (3.0-24.3 per 10,000 births). Most studies found a statistically significant decline in the number of NTDs between pre- and post-fortification periods, demonstrating that fortifying flour with folic acid reduced the NTD prevalence.

Studies in the United States have shown declines in the prevalence of overall NTDs (19%-35%) since the implementation of folic acid fortification in 1998^{14,15,16,17,18,19,42}.

Significant decreases in the occurrence of NTDs after folic acid fortification began were also reported in Argentina^{20,21}, Australia^{19,41}, Brazil^{20,22,23}, Canada^{19,24,25,26,27,28}, Chile^{20,29,30,31}, Costa Rica^{32,33}, Iran³⁴, Jordan³⁵, Peru³⁶, Saudi Arabia³⁷, and South Africa³⁸

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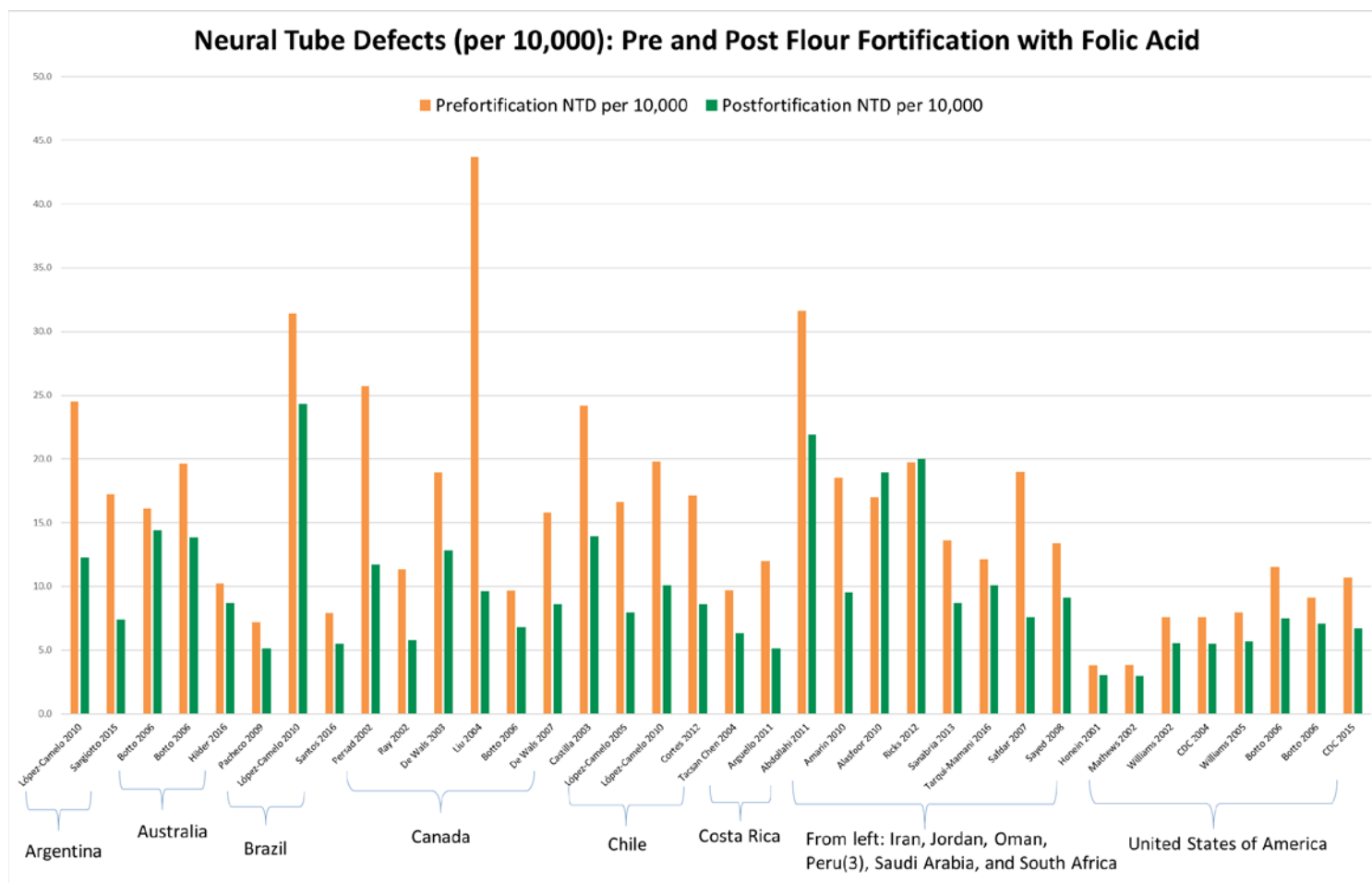
(1%-78%). The magnitude of the decrease in NTD prevalence varied; countries with higher baseline prevalence had greater declines.

The folate level of women before fortification and the number of women consuming fortified foods, together with the quality of surveillance systems, could affect the decline of NTD prevalence². Some researchers found an increase in NTD prevalence post-fortification, yet potential study limitations should be taken into consideration when interpreting the results. A study from Oman showed an 11% increase in the number of overall NTDs, and at the same time showed an 88% decrease in spina bifida³⁹. One plausible explanation is an improvement in the NTD screening process.

WHO estimates that 5-6 NTDs per 10,000 is the lowest level to be expected after women have optimum folate levels due to folic acid supplementation and/or fortification⁴⁰. As noted in the figure below, some studies in Brazil, Canada, Costa Rica, and the USA found the post-fortification NTD level to be 6 per 10,000 or lower. Other studies where more than 6 NTDs per 10,000 were found after fortification indicate room for improving women's folate status at the national or regional level.

In summary, existing evidence suggests that fortifying flour with folic acid contributes to reducing the number of NTDs.

Figure. A review of 36 documents that reported the prevalence of NTDs per 10,000 births* before and after the initiation of flour fortification with folic acid in 13 countries.



* The denominator can include live births, still births or terminations.

- ¹ World Health Organization, & Centers for Disease Control and Prevention. (2014). Birth defects surveillance: a manual for programme managers.
- ² Crider, K. S., Bailey, L. B., & Berry, R. J. (2011). Folic acid food fortification—its history, effect, concerns, and future directions. *Nutrients*, 3(3), 370-384.
- ³ Christianson, A., Howson, C. P., & Modell, B. (2006). March of Dimes: Global Report on Birth Defects—The Hidden Toll of Dying and Disabled Children. March of Dimes Birth Defects Foundation. White Plains, NY:(2006). *Clin Chim Acta*, 315, 99-110.
- ⁴ Blencowe, H., Cousens, S., Modell, B., & Lawn, J. (2010). Folic acid to reduce neonatal mortality from neural tube disorders. *International journal of epidemiology*, 39(suppl_1), 110-121.
- ⁵ MRC (Medical Research Council) Vitamin Study Research Group. (1991). Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *The Lancet*, 338(8760), 131–137.
- ⁶ Arth, A., Kancherla, V., Pachón, H., Zimmerman, S., Johnson, Q., & Oakley, G. P. (2016). A 2015 global update on folic acid-preventable spina and anencephaly. *Birth Defects Research Part A: Clinical and Molecular Teratology*, 106(7), 520-529.
- ⁷ WHO. (2007). Prevention of neural tube defects. Standards for Maternal and Neonatal Care.
- ⁸ Czeizel, A. E., & Dudás, I. (1992). Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. *New England Journal of Medicine*, 327(26), 1832-1835.
- ⁹ Ray, J. G., Singh, G., & Burrows, R. F. (2004). Evidence for suboptimal use of periconceptional folic acid supplements globally. *BJOG: An International Journal of Obstetrics & Gynaecology*, 111(5), 399-408.
- ¹⁰ Thurman, A. R., Clark, M. R., & Doncel, G. F. (2011). Multipurpose prevention technologies: biomedical tools to prevent HIV-1, HSV-2, and unintended pregnancies. *Infectious diseases in obstetrics and gynecology*, 2011.
- ¹¹ Food Fortification Initiative (FFI). (2017). *Global Progress*. Retrieved from http://www.ffinetwork.org/global_progress/index.php
- ¹² Pachón, H., Kancherla, V., Handforth, B., Tyler, V., & Bauwens, L. (2013). Folic acid fortification of wheat flour: A cost-effective public health intervention to prevent birth defects in Europe. *Nutrition Bulletin*, 38(2), 201-209.
- ¹³ Berry, R. J., Mulinare, J., & Hamner, H. C. (2010). Folic acid fortification: neural tube defect risk reduction—a global perspective. *Folate in health and disease*, 179-204.
- ¹⁴ Honein, M. A., Paulozzi, L. J., Mathews, T. J., Erickson, J. D., & Wong, L. Y. C. (2001). Impact of folic acid fortification of the US food supply on the occurrence of neural tube defects. *Journal of the American Medical Association*, 285(23), 2981-2986.
- ¹⁵ Mathews, T. J., Honein, M. A., & Erickson, J. D. (2002). Spina bifida and anencephaly prevalence—United States, 1991–2001. *MMWR. Morbidity and Mortality Weekly Report Recommendations and Reports*, 51(RR-13), 9-11.
- ¹⁶ Williams, L. J., Mai, C. T., Edmonds, L. D., Shaw, G. M., Kirby, R. S., Hobbs, C. A., ... & Levitt, M. (2003). Prevalence of spina bifida and anencephaly during the transition to mandatory folic acid fortification in the United States. *Obstetrical & gynecological survey*, 58(2), 90-92.
- ¹⁷ Centers for Disease Control and Prevention (CDC). (2004). Spina bifida and anencephaly before and after folic acid mandate—United States, 1995-1996 and 1999-2000. *MMWR. Morbidity and Mortality Weekly Report Recommendations and Reports*, 53(17), 362.
- ¹⁸ Williams, L. J., Rasmussen, S. A., Flores, A., Kirby, R. S., & Edmonds, L. D. (2005). Decline in the prevalence of spina bifida and anencephaly by race/ethnicity: 1995–2002. *Pediatrics*, 116(3), 580-586.
- ¹⁹ Botto, L. D., Lisi, A., Bower, C., Canfield, M. A., Dattani, N., De Vigan, C., ... & Lowry, R. B. (2006). Trends of selected malformations in relation to folic acid recommendations and fortification: an international assessment. *Birth Defects Research Part A: Clinical and Molecular Teratology*, 76(10), 693-705.
- ²⁰ López-Camelo, J. S., Castilla, E. E., & Orioli, I. M. (2010). Folic acid flour fortification: impact on the frequencies of 52 congenital anomaly types in three South American countries. *American Journal of Medical Genetics Part A*, 152(10), 2444-2458.
- ²¹ Sargiotto, C., Bidondo, M. P., Liascovich, R., Barbero, P., & Groisman, B. (2015). Descriptive study on neural tube defects in Argentina. *Birth Defects Research Part A: Clinical and Molecular Teratology*, 103(6), 509-516.
- ²² Santos, L. M., Lecca, R. C., Cortez-Escalante, J. J., Sanchez, M. N., & Rodrigues, H. G. (2016). Prevention of neural tube defects by the fortification of flour with folic acid: a population-based retrospective study in Brazil. *Bulletin of the World Health Organization*, 94(1), 22-29.
- ²³ Pacheco, S. S., Braga, C., Souza, A. I. D., & Figueiroa, J. N. (2009). Effects of folic acid fortification on the prevalence of neural tube defects. *Revista de Saúde Pública*, 43(4), 565-571.
- ²⁴ Persad, V. L., Van den Hof, M. C., Dubé, J. M., & Zimmer, P. (2002). Incidence of open neural tube defects in Nova Scotia after folic acid fortification. *Canadian Medical Association Journal*, 167(3), 241-245.
- ²⁵ Ray, J. G., Meier, C., Vermeulen, M. J., Boss, S., Wyatt, P. R., & Cole, D. E. (2002). Association of neural tube defects and folic acid food fortification in Canada. *The Lancet*, 360(9350), 2047-2048.

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- ²⁶ De Wals, P., Rusen, I. D., Lee, N. S., Morin, P., & Niyonsenga, T. (2003). Trend in prevalence of neural tube defects in Quebec. *Birth Defects Research Part A: Clinical and Molecular Teratology*, 67(11), 919-923.
- ²⁷ Liu, S., West, R., Randell, E., Longerich, L., O'Connor, K. S., Scott, H., ... & McCourt, C. (2004). A comprehensive evaluation of food fortification with folic acid for the primary prevention of neural tube defects. *BioMedical Central pregnancy and childbirth*, 4(1), 20.
- ²⁸ De Wals, P., Tairou, F., Van Allen, M. I., Uh, S. H., Lowry, R. B., Sibbald, B., ... & Fernandez, B. (2007). Reduction in neural-tube defects after folic acid fortification in Canada. *New England Journal of Medicine*, 357(2), 135-142.
- ²⁹ Castilla, E. E., Orioli, I. M., Lopez-Camelo, J. S., Dutra, M. D. G., & Nazer-Herrera, J. (2003). Preliminary data on changes in neural tube defect prevalence rates after folic acid fortification in South America. *American Journal of Medical Genetics Part A*, 123(2), 123-128.
- ³⁰ López-Camelo, J. S., Orioli, I. M., Dutra, M. D. G., Nazer-Herrera, J., Rivera, N., Ojeda, M. E., ... & Castilla, E. E. (2005). Reduction of birth prevalence rates of neural tube defects after folic acid fortification in Chile. *American Journal of Medical Genetics Part A*, 135(2), 120-125.
- ³¹ Cortés, F., Mellado, C., Pardo, R. A., Villarroel, L. A., & Hertrampf, E. (2012). Wheat flour fortification with folic acid: changes in neural tube defects rates in Chile. *American Journal of Medical Genetics Part A*, 158(8), 1885-1890.
- ³² Luis, T. C., & Melany, A. R. (2004). The Costa Rican experience: reduction of neural tube defects following food fortification programs. *Nutrition Reviews*, 62(6), S40-43.
- ³³ Argüello, B., de la Paz, M., & Umaña Solís, L. M. (2011). Impact of the fortification of food with folic acid on neural tube defects in Costa Rica. *Revista Panamericana de Salud Pública*, 30(1), 1-6.
- ³⁴ Abdollahi, Z., Elmadfa, I., Djazayeri, A., Golalipour, M. J., Sadighi, J., Salehi, F., & Sharif, S. S. (2011). Efficacy of flour fortification with folic acid in women of childbearing age in Iran. *Annals of Nutrition and Metabolism*, 58(3), 188-196.
- ³⁵ Amarín, Z. O., & Obeidat, A. Z. (2010). Effect of folic acid fortification on the incidence of neural tube defects. *Paediatric and perinatal epidemiology*, 24(4), 349-351.
- ³⁶ Sanabria Rojas, H. A., Tarqui-Mamani, C. B., Arias Pachas, J., & Lam Figueroa, N. M. (2013). Impacto de la fortificación de la harina de trigo con ácido fólico en los defectos del tubo neural, en Lima, Perú. In *Anales de la Facultad de Medicina*, 74(3), 175-180.
- ³⁷ Safdar, O. Y., Al-Dabbagh, A. A., AbuElieneen, W. A., & Kari, J. A. (2007). Decline in the incidence of neural tube defects after the national fortification of flour (1997-2005). *Saudi medical journal*, 28(8), 1227.
- ³⁸ Sayed, A. R., Bourne, D., Pattinson, R., Nixon, J., & Henderson, B. (2008). Decline in the prevalence of neural tube defects following folic acid fortification and its cost-benefit in South Africa. *Birth Defects Research Part A: Clinical and Molecular Teratology*, 82(4), 211-216.
- ³⁹ Alasfoor, D., Elsayed, M. K., & Mohammed, A. J. (2010). Spina bifida and birth outcome before and after fortification of flour with iron and folic acid in Oman. *Eastern Mediterranean Health Journal*, 16(5), 533-538.
- ⁴⁰ World Health Organization. (2015). Guideline: optimal serum and red blood cell folate concentrations in women of reproductive age for prevention of neural tube defects.
- ⁴¹ Hilder L. (2016). Neural Tube Defects in Australia, 2007-2011: Before and after implementation of the mandatory folic acid fortification standard. National Perinatal Epidemiology and Statistics Unit, University of New South Wales.
- ⁴² Williams, J., Mai, C.T., Mulinare, J., et al. Updated Estimates of Neural Tube Defects Prevented by Mandatory Folic Acid Fortification — United States, 1995–2011. *MMWR Morb Mortal Wkly Rep* 2015;64:1-5.