Evidence update: Weekly iron and folic acid supplementation (WIFAS) for adolescent girls and women

Potential to reduce anaemia and prevent neural tube defect affected pregnancies

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Background

WHAT ARE WIFAS?

Iron deficiency anaemia is the number one cause of lost disability adjusted life years (DALYS) in adolescent girls (10-19 years) globally.[1] Many countries are implementing weekly iron and folic acid supplementation (WIFAS) as it is an effective intervention to prevent and reduce anaemia.[2] The World Health Organization (WHO) recommends WIFAS containing 60 mg elemental iron and 2.8 mg folic acid be provided to menstruating adolescents (10-19 yrs) and women (20-49 yrs) living in areas where the prevalence of anaemia is greater than 20%.[2] To improve supplementation adherence and iron absorption, WIFAS are recommended to be provided once weekly, following the school semester, or for three months of once weekly supplementation, followed by three months of no supplementation, after which supplements should restart.[2] Most countries find following the school calendar most feasible, with supplementation once weekly while students are in session and breaks from supplementation when schools are closed for breaks or holidays.

FOLIC ACID IN WIFAS

The WHO recommendation to include 2.8 mg of folic acid in WIFAS aims to prevent neural tube defects (NTDs) and improve folate status.[2] This dose was chosen because it is seven times greater than the daily dose found effective in preventing NTDs (0.4 mg/day).[2] However, this WIFAS dose was not readily available in supply and is not included in the 22nd WHO Model Essential Medicines List (EML).[9] In the interim, most WIFAS programs are currently using 60 mg iron + 0.4 mg folic acid, which is the same dose as the recommended daily supplement during pregnancy,[10] a product which is more readily available.

The WHO-recommended WIFAS formulation with 2.8mg folic acid has not been included on the WHO EML as evidence was unavailable to support its effectiveness in preventing NTDs. Recently, a randomized control trial supported by Nutrition International aimed to fill this evidence gap by determining if WIFAS, formulated with 2.8 mg folic acid, would be more effective in reducing NTDs than the interim dose of 0.4 mg folic acid.[11]

Neural tube defects and folic acid

NTDs, such as spina bifida and anencephaly, are severe birth defects associated with neonatal mortality, morbidity, and long-term disability.[3] In addition, the treatment for NTDs is often costly, involving surgery, medication, and physiotherapy, services which are not available for many.[3] In 2015, there were an estimated 260,100 NTD-affected pregnancies, with 117,900 resulting in under-five deaths globally, resulting in one in every 500 births affected.[3,4]

Periconceptional folic acid can effectively reduce the risk of NTD-affected pregnancies by improving maternal folate status prior to and in very early pregnancy.[5] However, half of all pregnancies are unplanned, and the neural tube closes within six weeks of pregnancy (~28 days after conception).[6] This is before many women know they are pregnant, which means they may not be consuming daily prenatal supplements with folic acid. Once the neural tube closes, the window of opportunity to prevent NTDs with folic acid intervention is lost. Adolescent girls are disproportionately at risk; in low- and middle-income countries, 10 million girls between 15-19 years old have unplanned pregnancies annually.[7,8]

New evidence to support WHO recommended WIFAS dose (60 mg iron and 2.8 mg folic acid) for prevention of NTDs

FOLIC ACID EFFICACY TRIAL

Nutrition International, with funds from Global Affairs Canada, supported a collaboration with: South Australia Health and Medical Research Institute, Australia; The University of British Columbia, Canada; and Universiti Putra Malaysia. A three-arm, double-blind, randomized controlled efficacy trial was conducted in 2019 using a sample of 331 non-pregnant women aged 18-45 years old in Malaysia.[11] The study aimed to examine the effect of WIFAS using two doses of folic acid compared with an iron only placebo on red blood cell (RBC) folate concentrations. RBC folate concentration was chosen as an outcome measure because it is an established biomarker for NTD risk and a measure of longer-term folate status.[5,12] The WHO guidelines recommend population RBC folate concentrations be above 906 nmol/L to prevent NTDs[5] or >748 nmol/L CDC laboratory methods.

Study population context

- No food fortification with folic acid
- Low vitamin supplementation
- Prevalence of anaemia > 20% girls and women 15-49 years
- Low prevalence of folate deficiency amongst study participants

RBC folate population cut-off

This study used an adjusted RBC folate population cut-off value recommended by the U.S. CDC which produced a lower cut-off value of >748 nmol/L for optimal NTD prevention. This value was equivalent to the recommended >906 nmol/L.

Study participants were randomly assigned to receive one of three interventions (**see Table 1**). A once weekly supplement was provided for 16 weeks, followed by a four week period with no supplementation. The four week break period aimed to assess how folate concentrations change without supplementation to simulate a pause in program delivery like school holidays.[11]

Table 1. Study treatment interventions

WHO-recommended WIFAS dose	Interim WIFAS dose	Placebo – iron only
60 mg elemental iron + 2.8 mg folic acid	60 mg elemental iron + 0.4 mg folic acid	60 mg iron + 0 mg folic acid

KEY STUDY FINDINGS

At 16 weeks, those who received WIFAS with 2.8 mg folic acid had a 271 nmol/L greater mean RBC folate than those who received 0.4 mg. Also, after 16 weeks of supplementation, 68% of participants receiving 2.8 mg folic acid had RBC folate concentrations above the recommended population levels for NTD prevention compared with only 8% of those receiving WIFAS with 0.4 mg folic acid and 4% who received iron only. At 20 weeks, RBC folate concentrations decreased in all treatment groups following four weeks without receiving supplementation. However, RBC folate was still found to be higher than the suggested mean population cut off in the 2.8 mg group (> 50%) than those receiving 0.4 mg (11%) (**Table 2**).

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than the suggested mean population cut off in the 2.8 mg group (> 50%) than those receiving 0.4 mg (11%) (**Table 2**).

At 16 weeks, the 2.8 mg group was seven times more likely to have RBC folate concentrations >748 nmol/L than the 0.4 mg folic acid group and 16 times the iron only group. Following the washout period, the 2.8 mg folic acid group was still four times more likely to have RBC folate >748 nmol/L than the 0.4 mg folic acid group.

Table 2. Number and per cent with RBC folate concentrations >748 nmol/L by treatment group at baseline, 16 and 20 weeks

Treatment	0 weeks (Baseline) n (%)	16 weeks n (%)	20 weeks (16 weeks supplementation + 4 weeks' washout) n (%)	P value
2.8 mg folic acid (n=111)	9 (8%)	74 (68%)	55 (53%)	< 0.0001
0.4 mg folic acid (n=110)	4 (4%)	9 (8%)	12 (11%)	0.03
0 mg folic acid (n=110)	**3 (3%)**	**4 (3%)**	**3 (3%)**	

Implications of new evidence for WIFAS programs

CONSIDERATIONS FOR WIFAS INTERVENTIONS

Dose of folic acid in WIFAS: The folic acid efficacy trial found that the WHO recommended formulation of WIFAS dose (60 mg iron and 2.8 mg folic acid) was seven times more effective in achieving optimal RBC folate concentrations for NTD prevention than WIFAS with 0.4 mg folic acid. While folate deficiency was low amongst study participants, there was an equal benefit of the 0.4 mg and 2.8 mg dose on anaemia reduction and improvement of iron status.[13] However, the potential to prevent both anaemia and NTDs through WIFAS emphasizes the importance of using WIFAS with 2.8 mg of folic acid in contexts where both anaemia and NTDs are public health concerns.

WIFAS program delivery schedule: During four weeks of no supplementation/wash out, RBC folate concentrations decreased in all intervention groups. This may suggest that the benefits of WIFAS to prevent NTDs may be reduced during longer breaks in program delivery.

Recommended population: Currently, most WIFAS programs are targeted toward adolescents aged 10-19 years old. However, expanding access to WIFAS for menstruating women (20-49 years) where program delivery platforms are available and there is a public health need may be favourable given the potential for WIFAS to reduce anaemia and NTD-affected pregnancy.

In an effort to improve the availability, accessibility and affordability of the WHO recommended WIFAS dose, countries could consider the cost-benefits of WIFAS with 2.8 mg folic acid as a NTD prevention strategy. This should be done within the context of available delivery platforms for reaching menstruating adolescent girls and women, population folate status, adolescent pregnancy rate, the prevalence of NTDs, and availability of population folic acid interventions like food fortification. For further information, see Frequently Asked Questions on WIFAS for adolescents.

INCLUDING WIFAS FORMULATED WITH 60 MG IRON AND 2.8 MG FOLIC ACID IN THE WHO MODEL ESSENTIAL MEDICINES LIST (EML)

Including the WHO-recommended WIFAS dose on the WHO model EML could improve its availability and affordability for use in WIFAS programs by guiding national EMLs and thus purchasing and supply management decisions.[14] Having a distinct product for the WIFAS intervention would also reduce the chance of supply stockouts from using the same supplement for WIFAS as the recommended daily supplement during pregnancy. The WHO EML is updated every two years, and applications are now open for the 2023 revision. Given the newly available evidence, Nutrition International will be supporting the inclusion of the recommended WIFAS dose in this year's review of the WHO EML.

REFERENCES

1. Global Accelerated Action for the Health of Adolescents (AA-HA!): guidance to support country implementation. Summary. Geneva: World Health Organization; 2017 (WHO/FWC/MCA/17.05). Licence: CC BY-NC-SA 3.0 IGO. https://apps.who.int/iris/rest/bitstreams/1084421/retrieve

2. WHO. Guideline: Intermittent iron and folic acid supplementation in menstruating women. Geneva, World Health Organization, 2011. http://whqlibdoc.who.int/publications/2011/9789241502023_eng.pdf

3. Blencowe, H., Kancherla, V., Moorthie, S., Darlison, M. W., & Modell, B. (2018). Estimates of global and regional prevalence of neural tube defects for 2015: a systematic analysis. *Annals of the New York Academy of Sciences*, *1414*(1), 31–46. https://doi.org/10.1111/nyas.13548

4. Kancherla, V., Botto, L. D., Rowe, L. A., Shlobin, N. A., Caceres, A., Arynchyna-Smith, A., Zimmerman, K., Blount, J., Kibruyisfaw, Z., Ghotme, K. A., Karmarkar, S., Fieggen, G., Roozen, S., Oakley, G. P., Jr, Rosseau, G., & Berry, R. J. (2022). Preventing birth defects, saving lives, and promoting health equity: an urgent call to action for universal mandatory food fortification with folic acid. *The Lancet. Global health*, *10*(7), e1053–e1057. https://doi.org/10.1016/S2214-109X(22)00213-3

5. WHO. Guideline: Optimal serum and red blood cell folate concentrations in women of reproductive age for prevention of neural tube defects. Geneva: World Health Organization; 2015. https://apps.who.int/iris/handle/10665/161988

6. Bearak J, Popinchalk A, Ganatra B, Moller AB, Tunçalp Ö, Beavin C, Kwok L, Alkema L. Unintended pregnancy and abortion by income, region, and the legal status of abortion: estimates from a comprehensive model for 1990-2019. Lancet Glob Health. 2020 Sep;8. https://doi.org/10.1016/S2214-109X(20)30315-6

7. Darroch J, Woog V, Bankole A, Ashford LS. Adding it up: Costs and benefits of meeting the contraceptive needs of adolescents. New York: Guttmacher Institute; 2016. https://www.guttmacher.org/sites/default/files/report_pdf/adding-it-up-adolescents-report.pdf

8. UNFPA. Girlhood, Not Motherhood: Preventing Adolescent Pregnancy Published by the United Nations Population Fund UNFPA, New York; 2015. https://www.unfpa.org/sites/default/files/pub-pdf/Girlhood_not_motherhood_final_web.pdf

9. World Health Organization. (WHO). (2021). World Health Organization Model List of Essential Medicines – 22nd List, 2021. Geneva: World Health Organization; 2021 (WHO/MHP/HPS/EML/2021.02). Licence: CC BY-NC-SA 3.0 IGO. https://apps.who.int/iris/rest/bitstreams/1374779/retrieve

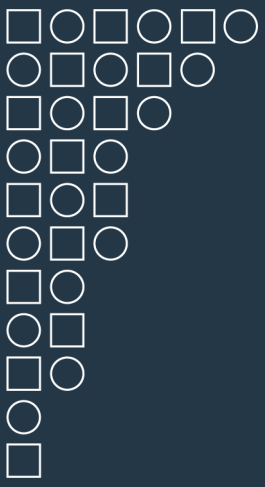
10. World Health Organization. (WHO). (2012). Guideline: Daily iron and folic acid supplementation in pregnant women. Geneva, World Health Organization, 2012. http://apps.who.int/iris/bitstream/10665/77770/1/9789241501996_eng.pdf

11. Samson, K. L., Loh, S. P., Lee, S. S., Sulistyoningrum, D. C., Khor, G. L., Shariff, Z. B. M., Ismai, I.Z., Yelland, L.N., Leemaqz, S., Makrides, M., Hutcheon, J.A., Roche, M.L., Karakochuk, C.D., Green, T. J. (2020). Weekly iron folic acid supplements containing 2.8 mg folic acid are associated with a lower risk of neural tube defects than the current practice of 0.4 mg: a randomised controlled trial in Malaysia. BMJ Global Health, 5 (12), doi:10.1136/bmjgh-2020-003897 https://dx.doi.org/10.1136%2Fbmjgh-2020-003897

12. Crider, K.S., Devine, O., Hao, L, et al. (2014). Population red blood cell folate concentrations for prevention of neural tube defects: Bayesian model. *BMJ,* 349:g4554. https://www.bmj.com/content/349/bmj.g4554

13. Samson KLI, Loh SP, Lee SS, Sulistyoningrum DC, Khor GL, Mohd Shariff ZB, Ismai IZ, Makrides M, Hutcheon JA, Roche ML, Green TJ, Karakochuk CD. The Inclusion of Folic Acid in Weekly Iron-Folic Acid Supplements Confers no Additional Benefit on Anemia Reduction in Nonpregnant Women: A Randomized Controlled Trial in Malaysia. J Nutr. 2021 Aug 7;151(8):2264-2270. doi: 10.1093/jn/nxab115. PMID: 33978167. https://doi.org/10.1093/jn/nxab115

14. Roche M, Samson K, Green T, Karakochuk C and Martinez H (2021). Weekly iron and folic acid supplementation (WIFAS): a critical review and rationale for inclusion in the essential medicines list to accelerate anemia and NTD reduction. Advances in Nutrition. 12 (2): 334-342. https://doi.org/10.1093%2Fadvances%2Fnmaa169



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