PERSPECTIVE

Perspective: Weekly Iron and Folic Acid Supplementation (WIFAS): A Critical Review and Rationale for Inclusion in the Essential Medicines List to Accelerate Anemia and Neural Tube Defects Reduction

Marion L Roche,[1] Kaitlyn LI Samson,[2,3] Tim J Green,[4,5] Crystal D Karakochuk,[2,3] and Homero Martinez[1,6]

[1] Global Technical Services, Nutrition International, Ottawa, Ontario, Canada; [2] Food, Nutrition, and Health, The University of British Columbia, Vancouver, British Columbia, Canada; [3] Healthy Starts, BC Children's Hospital Research Institute, Vancouver, British Columbia, Canada; [4] Women and Kids Theme, South Australia Health and Medical Research Institute, Adelaide, South Australia, Australia; [5] School of Medicine, University of Adelaide, Adelaide, South Australia, Australia; and [6] The Children's Hospital of Mexico, Mexico City, Mexico

ABSTRACT

Weekly iron and folic acid supplementation (WIFAS) is among the 8 key effective actions for improving adolescent nutrition included by the WHO in the 2018 guidelines. However, at present WIFAS in the WHO-recommended formulation is not included in the Model Essential Medicines List (MEML), limiting the potential for countries to import, produce, and prioritize this formulation as part of their national supply management and procurement plans for medicines. The WHO WIFAS guideline presents evidence that the formulation reduces anemia, but not that folic acid reduces neural tube defects (NTDs), because sufficient evidence was unavailable at the time of the last review. Recently, a 3-arm, parallel-group, randomized, double-blind, placebo-controlled folic acid efficacy trial on WIFAS was conducted to address this evidence gap. The study population included 331 women (18–45 y old), randomly assigned to 3 treatment groups, including a supplement with 60 mg Fe as ferrous fumarate and either 0 mg, 0.4 mg, or 2.8 mg of folic acid, to be consumed once weekly for 16 wk, followed by a 4-wk washout period. In this article we critically review how the outcomes of this folic acid efficacy trial, and how the evidence generated, could potentially be used to inform WHO WIFAS guidelines for the potential inclusion of this formulation on the MEML, and how this, in turn, may affect product availability. If the new evidence on weekly folic acid is assessed as adequately reducing the risk of NTDs, a guideline revision could be warranted and WIFAS could be presented to the MEML for the dual benefits of anemia reduction and NTD prevention. This inclusion could enable acceleration of implementing policies and programs to contribute to global anemia and NTD reduction efforts. *Adv Nutr* 2021;12:334–342.

Keywords: Essential Medicines List, Weekly Iron Folic Acid Supplementation (WIFAS), folic acid, neural tube defects, anemia

Introduction

Adolescent anemia

The World Health Assembly has called for a 50% reduction in anemia in women of reproductive age (aged 15–49 y) by 2025 (1). To reach this goal, the ~600 million adolescent girls living in developing countries should become a prime focus of anemia reduction efforts. Although adolescent-specific data are lacking globally, it is estimated that ~30% of adolescents are anemic (2). Iron deficiency anemia is now recognized as the number 1 cause of lost disability-adjusted life years in adolescent girls aged 10–19 y and boys aged 10–14 y globally (3).

Anemia has 3 major consequences for adolescent girls: *1*) decreased school performance (and challenges in concentration); *2*) loss of productivity (e.g., helping with younger siblings, agricultural work, wage labor, or community activities); and *3*) decreased current and future reproductive health for those that become pregnant (4). Related to this, young maternal age increases the risk of maternal anemia during pregnancy (5, 6). Although birth rates have declined in low-resource countries over the past 2 decades, adolescent birth rates have not seen the same decreases. Globally, 11% of all births are by adolescent girls (15–19 y old), with 95% of these in low-resource countries, leading to an increased risk of

 Adv Nutr 2021;12:334–342; doi: https://doi.org/10.1093/advances/nmaa169.

adverse outcomes for the adolescent mother and her child (7).

Intermittent (i.e., weekly) iron and folic acid supplementation is one of the few nutrition interventions shown to be effective among studies of anemia reduction programs in the Asia region. The WHO recommends intermittent iron and folic acid supplementation (at least once weekly for 3 mo, administered twice yearly, or after the school semester) as an effective strategy to prevent anemia in populations where anemia prevalence in women of reproductive age is of public health concern (anemia >20%) (8). The WHO Effective Actions for Adolescent Nutrition include weekly iron and folic acid supplementation (WIFAS) as 1 of 8 key effective actions for improving adolescent nutrition.

The Global Strategy for Women's, Children's and Adolescents' Health (2016–2030) highlights adolescents as a priority group for reaching the Sustainable Development Goals (1). However, adolescent nutrition has been an area previously neglected in global and national investment, policy, and programming in developing countries.

What is the Essential Medicines List and why does it matter for nutrition?

The WHO's Model Essential Medicines List (MEML) was first created in 1977 to guide the selection of medicines, including nutritional supplements, for the priority health care needs of the population (8). The selection of essential medicines is based upon the prevalence of disease and public health relevance; evidence of clinical efficacy and safety; as well as the comparative cost and subsequent cost-effectiveness. The inclusion of a medicine in this list implies that it should be available at all times, in adequate amounts, within a functioning health care system (9). Essential medicines should also be available in the appropriate dosage forms, with assured quality, and at a price point both individuals and communities can afford.

The MEML was not designed as a global standard, but rather as a guide for the development of national essential medicines lists (EMLs) and institutional EMLs. Since its creation, many countries have developed their own EMLs and some even have provincial or state lists. These lists are closely tied to national health care guidelines for clinical health care practice (9). Lists of essential medicines guide the procurement and supply of medicines in the public sector, schemes that reimburse medicine costs, medicine donations, and local medicine production. When adapting or translating the MEML to a national EML, countries often consider local demography, disease patterns, health care facilities, health care personnel training, and the availability of pharmaceutical products, financial resources, and environmental factors (2). With this in mind, many international organizations commonly use the essential medicines concept and base their supply system on the MEML (9). Implementing a supplementation intervention, such as micronutrient supplementation, depends on commodity availability. If a micronutrient supplement is on the MEML, its supply management is prioritized.

Currently, WIFAS is recommended by the WHO in the formulation of 60 mg Fe and 2.8 mg folic acid for anemia prevention. However, this formulation is not currently in the MEML. Increasing numbers of countries are looking for ways to improving adolescent nutrition, and WIFAS is one of the few interventions supported by effectiveness data. Many governments are interested in this intervention as part of anemia reduction strategies (10), so challenges arise when WIFAS in the 60 mg Fe and 2.8 mg folic acid WHO-recommended formulation is not available or accessible.

In the present article, we focus on the case of WIFAS as recommended in the WHO intermittent iron folic acid supplementation guideline (11), and the gaps in data that have prevented the commodity from being included in the MEML (12, 13). Further, we explore how data from a randomized controlled efficacy trial could be used to inform its inclusion in the MEML, and some of the practical consequences derived from it.

How medicines are added to the list and how this has changed over time

In 1999, the Expert Committee decided that the process by which the MEML was updated should be changed to reflect the advances in the science of evidence-based decision making, the link between essential medicines and guidelines for clinical health care, and the high cost of new medicines. The Committee moved that a more systematic approach be used for applications to the MEML. This represented a change from an "experience-based" approach, wherein selection decisions were made by members of the Expert Committee through applications from WHO program staff and the pharmaceutical industry (14). In addition, a more transparent process was initiated that allowed for interested parties to comment on the applications and draft recommendations (15). Different WHO departments also became involved in the application and selection process and a new WHO essential medicines library was developed. Overall, these actions aim to ensure that the Expert Committee operates with full scientific independence when making its final recommendations.

The current standard is that the MEML is updated every 2 y, reflecting the need to incorporate updates in the available evidence and new therapeutic options, while also accounting for changing therapeutic needs (15). The current list is the 21st iteration and was prepared by the WHO Expert Committee in June 2019 (16).

Supported by Nutrition International with a grant from Global Affairs Canada.
Author disclosures: The authors report no conflicts of interest.
Perspective articles allow authors to take a position on a topic of current major importance or controversy in the field of nutrition. As such, these articles could include statements based on author opinions or point of view. Opinions expressed in Perspective articles are those of the author and are not attributable to the funder(s) or the sponsor(s) or the publisher, Editor, or Editorial Board of Advances in Nutrition. Individuals with different positions on the topic of a Perspective are invited to submit their comments in the form of a Perspectives article or in a Letter to the Editor.
Address correspondence to HM (e-mail: hmartinez@nutritionintl.org).
Abbreviations used: EML, Essential Medicines List; MEML, Model Essential Medicines List; NTD, neural tube defects; RR, risk ratio; UI, uncertainty interval; WIFAS, weekly iron and folic acid supplementation.

The selection of new additions to the MEML depends on many factors, namely the disease burden and accurate data on efficacy, safety, and comparative cost-effectiveness. Data on stability, the need for special diagnostic or treatment facilities, or pharmacokinetic properties may also be considered if available and appropriate (15). Should accurate scientific data not be available, the decision may be deferred until more evidence is available, or expert opinion and experience may be used. The majority of essential medicines consist of a single product (e.g., a micronutrient), although combinations of products in specific formulations may be included when a proven advantage has been shown with regards to therapy, safety, or adherence when compared with single compounds given separately (15).

Current WHO guidelines regarding WIFAS

In 2011, the WHO released guidelines for *Intermittent Iron and Folic Acid Supplementation in Menstruating Women* that were developed by the Nutrition Guidance Expert Advisory Group (11). The WHO recommended that intermittent iron and folic acid supplementation be used as a public health intervention to improve iron status in menstruating adolescent girls and women living in areas where the prevalence of anemia in women of reproductive age (15–49 y of age) is >20% and no other micronutrient interventions are in place to control anemia.

The current guidelines state that the supplement should be taken once weekly for a period of 3 mo, followed by a 3-mo period with no supplementation. After this, supplementation should restart (11). Alternatively, if feasible, supplements could be given throughout the school or calendar year. WIFAS should contain 60 mg of elemental iron (which may be provided by 300 mg ferrous sulfate, 180 mg ferrous fumarate, or 500 mg ferrous gluconate) in addition to 2.8 mg of folic acid (the synthetic form of folate). This supplement should be available in tablet or capsule form and administered orally (11). In areas where malaria is endemic, WIFAS should be given along with measures to prevent, diagnose, and treat malaria (11). Because WIFAS is a preventative strategy, any woman diagnosed with anemia in a clinical setting should receive daily iron (120 mg elemental iron) and folic acid (0.4 mg) until her hemoglobin concentrations return to normal (17). Subsequently, she can then switch to an intermittent regimen to prevent anemia recurrence. This preventative measure could also be administered to women planning to become pregnant to reduce anemia and improve iron stores. However, upon confirmation of pregnancy, women should receive standard antenatal care of daily supplementation with iron and folic acid as a public health approach or where available in response to any clinical assessment on anemia and iron status (11, 18).

Rationale for a weekly supplementation schedule

An intermittent (i.e., weekly) iron supplementation schedule was proposed as an alternative to the usual daily dose because of the limited absorptive capacity of the intestinal cells, which leads to an accumulation of nonabsorbed iron in the intestinal mucosa and subsequent side effects. Given that intestinal cells turn over every 5–6 d, an intermittent supplementation regime would expose only new cells to the iron compound, leading to increased absorption and reduced iron exposure, decreasing subsequent oxidative stress (19, 20). This could minimize absorptive competition between iron and other minerals, and reduce some of the unpleasant side effects associated with daily supplementation (21, 22). With respect to the latter, intermittent supplementation programs have been shown to increase adherence and acceptability among participants (23, 24).

The weekly dose of 2.8 mg folic acid was chosen because it was 7 times the daily dose (0.4 mg) found to be effective in reducing the risk of NTDs in clinical trials (25). Although studies examining the effect of weekly folic acid have found that it is effective in increasing RBC folate and plasma folate concentrations (26), a rigorous trial had not been conducted to assess if 2.8 mg folic acid/wk is the optimal dose to allow women to reach an RBC folate concentration associated with a low risk of NTDs (>906 nmol/L) (27).

TABLE 1 Alternative iron salts to provide the concentration of iron recommended on the Essential Medicines List

Ferrous salt formulation	60 mg elemental iron equivalent dose
Ferrous sulfate heptahydrate	300 mg
Ferrous fumarate	180 mg
Ferrous gluconate	500 mg

Current formulations of iron and folic acid on the EML

Ferrous salt.

Currently, iron salt is listed on the WHO MEML under "Section 10.1. Antianaemia medicines." It is recommended in either oral liquid or tablet form. The oral liquid form should be equivalent to 25 mg Fe (as sulfate)/mL, whereas the tablet form should contain 60 mg Fe (16). This amount of iron in tablet form may be provided by different concentrations of iron salts, as **Table 1** shows.

Folic acid.

In 2015, the 19th WHO MEML welcomed the addition of daily 0.4 mg folic acid tablets for periconceptional use in women of reproductive age. This dose of folic acid was included as a public health intervention to prevent the first occurrence of NTDs and is listed under "Section 10.1. Antianemia medicines" (28).

An inverse relation between RBC folate and risk of NTDs has been demonstrated. In 1995, a case-control study in Ireland assessed the relation between both plasma folate and RBC folate and the risk of an NTD-affected pregnancy (29). In this study, researchers examined blood samples taken at ∼15 weeks of gestation (median value) from 84 cases and 266 controls and followed women until delivery. It was found that the risk of NTDs was inversely associated with maternal RBC folate concentrations in early pregnancy. A

low risk (8 per 10,000 births) was associated with an RBC folate concentration >906 nmol/L, but there was a risk reduction across the entire range of RBC folate. Overall, there was a >8-fold difference in risk of NTD-affected pregnancy between women with RBC folate >906 nmol/L and those with RBC folate <340 nmol/L ($P < 0.001$) (29). This was later confirmed in 2014 when the Community Intervention Project (1993–1995; $n = 247{,}831$) and Folic Acid Dosing trial (2003–2005; $n = 1194$) found that the "optimal" population RBC folate concentration for the prevention of NTDs was ~1000 nmol/L (30). The cutoff of 906 nmol/L is used to identify folate *insufficiency for NTD prevention*. It should be noted that the threshold for *insufficient* folate concentration (i.e., the concentration above which there is optimal protection against the risk of NTD) is higher than the 305 nmol/L used to identify those at risk of folate deficiency anemia (31).

That periconceptional folic acid supplementation reduces NTD risk is beyond refute and is summarized in a 2014 Cochrane systematic review (26). The review included 5 high-quality studies, including 6708 births, and reported that daily folic acid supplementation (where supplement doses included were 0.36 mg, 0.8 mg, 2 mg, and 4 mg folic acid) had a protective effect for the prevention of NTDs compared with no intervention/placebo or other minerals without folic acid [risk ratio (RR): 0.31; 95% CI: 0.17, 0.58]. Folic acid was also found to have a significant protective effect on the recurrence of NTDs (RR: 0.34; 95% CI: 0.18, 0.64) in an analysis that included 4 studies and 1846 births (26). In a subgroup analysis the authors of this report concluded that daily doses >0.4 mg conferred no additional benefit on the reduction of NTD occurrence and it did not matter whether folic acid was consumed alone or as part of a multiple micronutrient formulation (26). It should be noted that the WHO-recommended once-weekly iron folic acid formulation containing 60 mg Fe and 2.8 mg folic acid was not included in this review.

In addition, it should also be noted that for women at high risk of an NTD-affected pregnancy, such as women with a previous NTD-affected pregnancy (32), the recommended dose of folic acid is much higher (5 mg folic acid daily). This formulation is currently included on the WHO MEML.

Ferrous salt and folic acid.

Currently, the combination of a ferrous salt and folic acid is listed on the WHO MEML under "Section 10.1. Antianaemia medicines." The formulation listed includes 60 mg Fe and 0.4 mg folic acid for use as a nutritional supplement during pregnancy (28). It is intended to be used as a daily oral supplement to prevent maternal anemia, puerperal sepsis, low birth weight, and preterm birth (33).

The WHO makes a distinction between "supplementation," meant to prevent anemia by improving iron status before iron deficiency anemia is manifest, and "therapeutic supplementation," meant to correct (treat) established iron deficiency anemia. The first intervention may be delivered by community-based initiatives such as women's organizations, schools, religious and community leaders, or self-administered; the second one should be part of the health care delivery system.

The recommended formulation for prevention of iron deficiency anemia (i.e., low hemoglobin and low ferritin) in women of reproductive age, as listed in the WHO guideline, is daily supplementation with 30–60 mg Fe and 0.4 mg folic acid for a period of 3 mo (34). Although this approach is effective, success from a public health perspective is often hampered by low coverage rates, insufficient tablet distribution, and low adherence due to unpleasant side effects (e.g., constipation, dark stools, and metallic taste), lack of diagnosis, and low feasibility of screening (11). Most commonly, inadequate supply, not adverse side effects, has been noted as the primary reason women did not consume their supplements (35, 36). This has been regarded by health care providers as a problem of inadequate procurement procedures at the local level as opposed to upper or central levels (35). Side effects have been noted to only affect adherence minimally because the proportion of women who stop taking the supplements is small and is not seen as a reason for program failure (36).

Review of the evidence to support inclusion of WIFAS on the EML.

In 2013, an application was made to the WHO MEML to include an intermittent regime of a fixed-dose combination of 60 mg elemental iron and 2.8 mg folic acid to be used by menstruating women and adolescent girls in areas where the prevalence of anemia is moderate or high (i.e., >20% in the population) (12). Evidence to support this application came from a 2011 Cochrane review that found that, compared with no supplementation or placebo, women taking intermittent iron supplements had improved hemoglobin and ferritin concentrations, and were less likely to develop anemia (36). There was variability in data quality, however; when compared with data from eligible trials of daily iron supplementation, women using intermittent supplements were more likely to be anemic and have lower ferritin concentrations, despite having similar hemoglobin concentrations (37). Therefore, the Expert Committee did not support the application to the MEML, because the data to support this recommendation did not show that the intermittent regime was at least as effective as the daily fixed dose combination (60 mg Fe and 0.4 mg folic acid) for the prevention and control of anemia in menstruating women (12, 13).

In 2015, a new application was made to the 19th WHO MEML for this WIFAS formulation of ferrous salt and folic acid on behalf of the WHO Department of Nutrition for Health and Development. This application included additional data on the efficacy of weekly folic acid on improving RBC folate status for the prevention of NTDs (13). Evidence from 2 clinical trials was included in the application, showing the effects of once-weekly (2.8 mg or 4 mg) compared with daily folic acid supplementation (where daily doses included 0.1 mg, 0.4 mg, and 4 mg) on RBC

folate concentrations (38, 39). The studies presented found that after 12 wk, weekly 2.8 mg folic acid supplementation increased RBC folate concentrations to 900 nmol/L (95% CI: 828, 978 nmol/L), whereas after 6 mo, 4 mg folic acid/wk raised RBC folate concentrations to 888.6 nmol/L (95% CI: 840.1, 939.9 nmol/L) (38, 39). The rise in RBC folate concentrations was linear and did not reach a plateau in the study time frame. Both of these concentrations are close to 906 nmol/L, corresponding to the concentration associated with the largest reduction in risk of NTDs (29). However, both weekly folic acid supplementation schedules produced lower plasma folate and RBC folate concentrations than did daily supplementation. Therefore, the Expert Committee determined that weekly folic acid supplementation (either 2.8 mg or 4 mg) was not as effective as daily supplementation with 0.4 mg for the prevention of NTDs (13).

The Expert Committee considered that the strength of the evidence presented ranged from low to moderate, and considered it insufficient to recommend the addition to the MEML of the new fixed-dose combination formulation of ferrous salt plus folic acid (60 mg and 2.8 mg), for either the prevention of anemia or the reduced risk of NTDs (13). Two other issues that the Committee reported were the lack of adequate adherence data along with the fact that the commercial availability of the product at the time of the report was limited to 1 country (13).

How to improve the evidence to support the potential inclusion of WIFAS on the MEML

In 2019, an efficacy trial, titled "Effect of once weekly folic acid supplementation on erythrocyte folate concentrations in women to determine potential to prevent neural tube defects: a randomised controlled dose-finding trial in Malaysia" (herein referred to as the Folic Acid Efficacy Trial), was conducted in order to provide evidence for the guideline on weekly folic acid supplementation in menstruating women (40). This trial was coordinated by Nutrition International, the South Australia Health and Medical Research Institute, Universiti Putra Malaysia, and the University of British Columbia. This trial took place in Selangor, Malaysia, where the prevalence of anemia among females was 35.5% according to the 2015 National Health and Morbidity Survey (41, 42). A previous study conducted in 2005, including 399 Malaysian women aged 18–40 y, showed that 15.1% had plasma folate deficiency (defined here as <6.8 nmol/L), whereas 9.3% had RBC folate deficiency (defined here as <363 nmol/L) (43). Only 15.2% of the women had RBC folate concentrations above the sufficiency threshold of 906 nmol/L.

Background for the study.

In 2015, the overall global estimated prevalence of NTD-affected birth outcomes was 260,100 [95% uncertainty interval (UI): 213,000, 322,000] (44). This estimate excluded spontaneous fetal loss and equates to 18.6 per 10,000 live births (95% UI: 15.3, 23.0 per 10,000 live births). Asia and Africa have the highest prevalence of NTD-associated stillbirths, representing 85% of the global prevalence. Within Malaysia, data from the 2009 Malaysian National Neonatal Registry found that, from a cohort of 141 infants with various NTDs, the prevalence was 4.2 per 10,000 live births (45). This, however, is likely an underestimate because the authors were unable to include information on stillbirths and abortions in the participating hospitals; data from home deliveries (~5% of the total births) and from private hospitals; and screening of all the unborn infants, using ultrasonography, to detect spina bifida occulta and other less obvious NTDs (45). In addition, a previous study by Green et al. (46) looked at the RBC folate status and predicted NTD rate in 3 Asian cities (Beijing, Kuala Lumpur, and Jakarta) and found that Kuala Lumpur, Malaysia, had a mean RBC folate concentration of 674 nmol/L (95% CI: 644, 704 nmol/L), which corresponded to a predicted NTD rate of 24 per 10,000 live births (95% CI: 22, 25 per 10,000 live births). It is relevant to mention that Malaysia does not have a folic acid food fortification program.

Study design.

This study included a total of 331 women (18–45 y of age), recruited from the local community surrounding Universiti Putra Malaysia. Inclusion criteria required that women were nonpregnant (self-reported), not planning on becoming pregnant, not currently taking micronutrient supplements containing folic acid or participating in another nutritional intervention, apparently healthy, not taking any medication known to affect folate status, and not planning to leave the community during the timeline of the study. The study protocol called for women found to have severe anemia (defined as hemoglobin <80 g/L) to be contacted within 3 d and referred to a local health center for follow-up, but they were not excluded from the study unless their medical practitioner recommended withdrawal (47). The study design corresponded to a 3-arm, parallel-group, randomized, double-blind, placebo-controlled trial with a 16-wk intervention period followed by a 4-wk washout period. The washout period was included to simulate a school break/vacation or break from supplementation to enable assessment of how folate concentrations changed in the period without supplementation, because the WHO suggests ≤3 mo without supplementation in the WIFAS guideline (11). Ethical approval was received from the Ethics Committee for Research Involving Human Subjects of Universiti Putra Malaysia (JKEUPM-2018-255) and the University of British Columbia Clinical Research Ethics Board (H18-00768).

Intervention.

Women were randomly assigned at the individual level to 1 of 3 treatment groups, including 2 intervention groups and a placebo. The treatment groups included a supplement with 60 mg Fe as ferrous fumarate and either 0 mg, 0.4 mg, or 2.8 mg folic acid, to be taken once weekly on a prespecified day for 16 wk. The rationale for the dosing schedule was based on the current RDA for folic acid for women of

reproductive age (0.4 mg/d) (31), and it is also the daily dose recommended to decrease the risk of an NTD-affected pregnancy (25). This formulation is commonly available on the market, because it is on the EML, and represents the current standard of care for women of reproductive age (11). The 2.8 mg folic acid/wk, corresponding to 7 times the daily dose (7 d × 0.4 mg/d), was chosen because it is the current WHO-recommended formulation for WIFAS. The tablet containing 0 mg folic acid corresponded to the placebo.

Outcome measures.

Fasting venous blood was collected at 0, 16, and 20 wk. The primary outcome measure was RBC folate at 16 wk. Secondary outcomes included RBC folate concentrations at 20 wk (after a 4-wk washout period) as well as plasma folate concentrations at 16 and 20 wk. The percentages of women with an RBC folate concentration ≥906 nmol/L (equivalent to the 748-nmol/L calibrator-adjusted concentration), associated with the highest protection at the population level against the risk of an NTD, after 16 wk of treatment and 4 wk of washout were also determined (29).

Discussion of how the results of the Folic Acid Efficacy Trial should influence the recommendation for WIFAS and the MEML

The Folic Acid Efficacy Trial helps address several of the concerns the Expert Committee had with the previous 2015 application involving a new formulation of ferrous salt and folic acid. Here, we also discuss considerations of additional supply and demand–related changes in the enabling environment. Such concerns include *1*) the insufficient amount of high-quality efficacy evidence, because there is a dearth of randomized clinical trials addressing this issue with a study sample sufficiently powered to evaluate the statistical significance of the differences under evaluation; *2*) the lack of adequately reported adherence data, which precluded a proper assessment of the effect of the intervention; and *3*) the commercial unattainability of the WHO-recommended weekly iron folic acid formulation (28). The study was designed so that if 1 or both of the weekly supplementation schemes proved effective at raising population RBC folate concentrations >906 nmol/L (29), the formulation could be considered for inclusion in the MEML, adding the potential of reducing the risk of NTDs in women of reproductive age to its role in the prevention of anemia. In this section we discuss potential implications for the availability and use of WIFAS and/or weekly iron supplementation.

Overview of the Folic Acid Efficacy Trial in Malaysia results.

In September 2019, a total of 324 women of the 331 women initially recruited completed the trial: 94% adherence. At 16 wk women receiving the WIFAS with 0.4 mg and 2.8 mg folic acid/wk had a higher mean RBC folate than those receiving iron only (0 mg folic acid). Moreover, women receiving the WIFAS with the 2.8 mg folic acid had a 271-nmol/L greater mean RBC folate than those receiving 0.4 mg ($P < 0.0001$). At 16 wk, 68% of women in the 2.8 mg group achieved RBC folate concentrations >906 nmol/L, values associated with a low risk of an NTD-affected pregnancy, compared with only 8% and 4% in the 0.4 mg and iron-only groups, respectively. This trial used a US CDC–endorsed assay, where a reading of 748 nmol/L is equivalent to the WHO-recommended cutoff of 906 nmol/L. For ease of interpretation, we report this value as >906 nmol/L. Most notably, women consuming the higher dose of weekly folic acid (2.8 mg) were 7 times more likely than those receiving 0.4 mg to achieve an RBC folate concentration >906 nmol/L ($P < 0.0001$).

After the 4-wk washout period, mean RBC folate fell in both groups receiving folic acid, but remained higher than in those receiving iron alone. Importantly, >50% of women receiving 2.8 mg had RBC folate concentrations >906 nmol/L compared with only 11% in those receiving 0.4 mg. Thus, after a school break of ≤4 wk of not taking folic acid, women receiving 2.8 mg folic acid as part of iron folic acid supplementation would still have protection against NTDs, whereas those who received 0.4 mg would not (48).

Effectiveness of 60 mg Fe and 2.8 mg folic acid to increase population RBC folate concentration > 906 nmol/L.

Because the results of the Folic Acid Efficacy Trial show that a significant proportion of the treatment group receiving 2.8 mg folic acid weekly had endline (16 wk) RBC folate concentrations significantly above the threshold associated with a low risk of NTDs (>906 nmol/L) (29), this may contribute the efficacy evidence needed for the WHO Expert Committee to consider its inclusion in the MEML upon resubmission.

The ability of the weekly treatment with 2.8 mg folic acid during 16 wk of supplementation to raise RBC folate concentrations to a concentration associated with the most reduced risk of NTDs for a significant proportion of the population would provide the EML application with additional high-quality efficacy evidence. This trial features a high-quality study design because it is a double-blind, randomized, placebo-controlled trial. In addition, the sample size is larger than that of the Norsworthy et al. (39) trial, which is the only other trial that has looked specifically at the effects of a weekly dose of 2.8 mg folic acid on RBC folate. The Folic Acid Efficacy Trial also measured adherence data associated with the trial protocol, which was promoted by weekly mobile text consumption reminders and active follow-up, addressing an additional concern posed by the Expert Committee for the MEML.

If the resubmission to the MEML is successful, this means there would be a new formulation of ferrous salt and folic acid present on the MEML. Not only would there be a new formulation present, but also there would be a new purpose listed. This formulation of ferrous salt and folic acid would be listed as a public health measure for the prevention of anemia with the added benefit of reducing the risk of NTDs.

At the time of the previous application, 20 low- and middle-income countries were surveyed and it was found that none of their NEMLs contained 60 mg Fe and 2.8 mg folic acid (49, 50). This was expected, because this formulation is not on the EML, and there was only 1 identified international supplier that produced this formulation (Laboratorios Prieto in Panama). Inclusion of this new formulation in the MEML could drastically change this. Because many countries base their national formularies on the WHO EML (9), the inclusion of 60 mg Fe and 2.8 mg folic acid could prompt more countries to acquire this formulation, giving more suppliers incentive to produce it. A recent development on the supply side of WIFAS in the WHO-recommended formulation is the inclusion of the 60 mg Fe and 2.8 mg folic acid combination in the UNICEF supply catalogue, as of 2019 (51). This product is listed as "anti-anaemic" and one of the purposes is "for the prevention of neural tube defects and other congenital malformations in the foetus." Having evidence of the dual benefits of anemia reduction and NTD prevention could possibly galvanize additional support and resources to implement and scale up WIFAS programs for adolescent girls, especially in countries with high rates of adolescent pregnancies. Delivery of WIFAS could also be expanded to women of reproductive age. An additional advantage to a unique product for WIFAS, that is a distinct formulation from the daily dose of iron folic acid for pregnant women, is a reduction in current challenges in supply management, which has required joint forecasting, procurement, and supply chain management. A distinct WIFAS formulation and product could help avoid the risks of stock outs that have occurred when adolescent nutrition programs have increased the demand for existing maternal iron and folic acid supply at national, subnational, or facility level.

Considerations for the dosing regime.

In a previous study, Norsworthy et al. (39) administered a weekly dose of 2.8 mg folic acid to women of reproductive age and evaluated its effect on RBC folate after 12 wk of treatment, with assessments at 6 and 12 wk. They found a linear response in RBC folate concentration during the intervention, and although half the sample achieved a RBC folate concentration >905 nmol/L at week 12, this concentration had not reached a plateau by the end of the study, raising the possibility that a higher proportion would have exceeded the threshold for greatest NTD risk-prevention had the study gone on for longer.

The results at 16 wk of supplementation in the current Folic Acid Efficacy Trial may also inform the dosing schedule for the WIFAS guideline.

Independently of the specific outcome of the trial, it will also be crucial to do further analyses to look at the effects of each treatment arm on anemia outcomes, focusing on hemoglobin and ferritin concentrations as well as on RBC folate, in order to evaluate the effect of the treatment on iron and folate deficiency anemias, separately and in conjunction.

Conclusions

WHO guidelines for nutrition supplements, especially those with multiple micronutrients such as iron and folic acid, are limited by a lack of availability of high-quality evidence. Due to the lack of high-quality evidence, some products are unlikely to be included in the MEML as well as in national and regional EMLs. This can create a situation where program guidance is not harmonized with supply, limiting potential implementation of effective interventions, such as WIFAS, for anemia prevention. This also limits the interest of global pharmaceutical suppliers to respond to demands from Ministries of Health, because without a clear market production they are deprioritized. Such is the case for WIFAS, because there has been clear evidence for anemia reduction but insufficient evidence for adherence, comparability with daily supplementation for anemia reduction, and potential to reduce the risk of NTDs. The updated evidence on WIFAS from the Folic Acid Efficacy Trial, showing the potential for population RBC folate to increase to concentrations associated with a reduced risk of NTDs, has potential to influence the WHO guidelines and the MEML. Harmonization between the WHO guidelines and MEML would provide an optimal opportunity for public health anemia reduction programs as well as NTD prevention.

Acknowledgments

The authors' responsibilities were as follows—MLR and CDK: are co-investigators on the clinical trial described; MLR: prepared the first draft of the paper; KLIS: is associate investigator on the trial described, contributed with the literature review for this paper, and contributed to drafting the paper; TJG: is principal investigator on the clinical trial described and contributed to the final write-up of this paper; CDK: contributed to the final draft of this paper; HM: coordinated the initial drafts and final write-up of this paper; and all authors: read and approved the final manuscript.

References

1. World Health Organization. Global strategy for women's, children's and adolescents' health 2016–2030. Geneva, Switzerland: WHO; 2016.
2. United Nations Children's Fund. Progress for children: a report card on adolescents. New York: UNICEF; 2012.
3. World Health Organization. Global Accelerated Action for the Health of Adolescents (AA-HA!) implementation guidance, 2016-2030[Internet]. Geneva (Switzerland): WHO; 2017. [Accessed 2020 Jul 20]. Available from: http://www.who.int/maternal_child_adolescent/topics/adolescence/aa-ha-guidance-full-draft.pdf.
4. Kraemer K, Zimmermann MB,editors. Nutritional anemia. Basel (Switzerland): Sight and Life Press; 2007.
5. Dean SV, Mason E, Howson CP, Lassi ZS, Imam AM, Bhutta ZA. Born too soon: care before and between pregnancy to prevent preterm births: from evidence to action. Reprod Health 2013;10(Suppl 1):S3.
6. World Health Organization. Adolescent pregnancy fact sheet. [Internet]. Geneva (Switzerland): WHO; 2014. [Accessed 2020 Jul 20]. Available from: http://apps.who.int/iris/bitstream/10665/112320/1/WHO_RHR_14.08_eng.pdf.
7. United Nations Population Fund. Motherhood in childhood: facing the challenge of adolescent pregnancy. State of the world population 2013. New York: United Nations Population Fund; 2013.

8. World Health Organization. Guideline: implementing effective actions for improving adolescent nutrition. [Internet]. Geneva (Switzerland): WHO; 2018. [Accessed 2020 Jul 20]. Available from: https://apps.who.int/iris/bitstream/handle/10665/260297/9789241513708-eng.pdf?sequence=1.
9. World Health Organization. Essential medicines and health products. [Internet]. Geneva (Switzerland): WHO; 2018. [Accessed 2020 Jul 20]. Available from: http://www.who.int/medicines/services/essmedicines_def/en/.
10. Nutrition International. The Right Start Initiative: accelerating women and girls' nutrition. [Internet]. Ottawa: Nutrition International; 2019. [Accessed 2020 Jul 20]. Available from: https://www.nutritionintl.org/news/all-blog-posts/a-year-of-action-for-nutrition-starts-today/. .
11. World Health Organization. Guideline: intermittent iron and folic acid supplementation in menstruating women. Geneva (Switzerland): WHO; 2011.
12. World Health Organization. The selection and use of essential medicines: report of the WHO Expert Committee, 2013 (including the 18th WHO model list of essential medicines and the 4th WHO model list of essential medicines for children). [Internet]. WHO Technical Report Series, No. 985. Geneva (Switzerland): WHO; 2013. [Accessed 2020 Jul 20]. Available from: https://apps.who.int/iris/bitstream/handle/10665/112729/WHO_TRS_985_eng.pdf?sequence=1.
13. World Health Organization. The selection and use of essential medicines: twentieth report of the WHO Expert Committee 2015 (including the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children).[Internet]. WHO Technical Report Series, No. 994. Geneva (Switzerland): WHO; 2015. [Accessed 2020 Jul 20]. Available from: http://apps.who.int/iris/bitstream/10665/189763/1/9789241209946_eng.pdf.
14. Laing R, Waning B, Gray A, Ford N, 't Hoen E. 25 years of the WHO essential medicines lists: progress and challenges. Lancet 2003;361(9370):1723–9.
15. World Health Organization. WHO medicines strategy: revised procedure for updating WHO's Model List of Essential Drugs: report by the Secretariat. [Internet]. Geneva (Switzerland): WHO; 2001. [Accessed 2020 Jul 20]. Available from: https://apps.who.int/iris/handle/10665/78389.
16. World Health Organization. WHO Model Lists of Essential Medicines. 21st List. [Internet]. Geneva (Switzerland): WHO; 2019. [Accessed 2020 Jul 20]. Available from: https://www.who.int/medicines/publications/essentialmedicines/en/.
17. Stoltzfus R, Dreyfuss M. Guidelines for the use of iron supplements to prevent and treat iron deficiency anemia. Washington (DC): ILSI Press; 1998.
18. World Health Organization. Guideline: daily iron and folic acid supplementation in pregnant women. Geneva (Switzerland): WHO; 2012.
19. Viteri FE, Liu X, Tolomei K, Martín A. True absorption and retention of supplemental iron is more efficient when iron is administered every three days rather than daily to iron-normal and iron-deficient rats. J Nutr 1995;125:82–91.
20. Wright A, Southon S. The effectiveness of various iron supplementation regimens in improving the Fe status of anemic rats. Br J Nutr 1990;63:579–85.
21. Angeles-Agdeppa I, Schultink W, Sastroamidjojo S, Gross R, Karyadi D. Weekly micronutrient supplementation to build iron stores in female Indonesian adolescents. Am J Clin Nutr 1997;66:177–83.
22. Viteri F, Berger J. Importance of pre-pregnancy and pregnancy iron status: can long-term weekly preventive iron and folic acid supplementation achieve desirable and safe status? Nutr Rev 2005;63(12):S65–76.
23. Casey G, Jolley D, Phuc T, Tinh T, Tho D, Montresor A, Biggs VA. Long-term weekly iron-folic acid and de-worming is associated with stabilised haemoglobin and increasing iron stores in non-pregnant women in Vietnam. PLoS One 2010;5(12):e15691.
24. Vir S, Singh N, Nigam A, Jain R. Weekly iron and folic acid supplementation with counseling reduces anemia in adolescent girls: a large-scale effectiveness study in Uttar Pradesh, India. Food Nutr Bull 2008;29(3):186–94.
25. Berry R, Li Z, Erickson J, Li S, Moore C, Wang H. Prevention of neural-tube defects with folic acid in China. N Engl J Med 1999;341(20):1485–90.
26. De-Regil L, Peña-Rosas J, Fernández-Gaxiola A, Rayco-Solon P. Effects and safety of periconceptional oral folate supplementation for preventing birth defects. Cochrane Database Syst Rev 2015;35(12):CD007950.
27. World Health Organization. Guideline: optimal serum and red blood cell folate concentrations in women of reproductive age for prevention of neural tube defects. Geneva (Switzerland): WHO; 2015.
28. World Health Organization. World Health Organization Model List of Essential Medicines. 20th List, 2017. [Internet]. Geneva (Switzerland): WHO; 2017. [Accessed 2020 Jul 20]. Available from: https://www.who.int/publications/i/item/eml-20.
29. Daly LE, Kirke PN, Molloy A, Weir DG, Scott JM. Folate levels and neural tube defects. Implications for prevention. JAMA 1995;274:1698–702.
30. Crider KS, Devine O, Hao L, Dowling NF, Li S, Molloy AM, Li Z, Zhu J, Berry RJ. Population red blood cell folate concentrations for prevention of neural tube defects: Bayesian model. BMJ 2014;349:g4554.
31. Institutes of Medicine. Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline. A Report of the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and its Panel on Folate, Other B Vitamins, and Choline and Subcommittee on Upper Reference Levels of Nutrients. Washington (DC): National Academy Press; 1998.
32. Douglas Wilson R, Audibert F, Brock J-A, Carroll J, Cartier L, Gagnon A, Johnson J-A, Langlois S, Murphy-Kaulbeck L, Okun N, et al. Pre-conception folic acid and multivitamin supplementation for the primary and secondary prevention of neural tube defects and other folic acid-sensitive congenital anomalies. J Obstet Gynaecol Can 2015;37(6):534–49.
33. World Health Organization. WHO recommendations on antenatal care for a positive pregnancy experience.[Internet]. Geneva (Switzerland): WHO; 2016. [Accessed 2020 Jul 20]. Available from: http://apps.who.int/iris/bitstream/10665/250796/1/9789241549912-eng.pdf.
34. World Health Organization. Guideline: daily iron supplementation in adult women and adolescent girls. Geneva (Switzerland): WHO; 2016.
35. Galloway R, McGuire J. Determinants of compliance with iron supplementation: supplies, side effects, or psychology? Soc Sci Med 1994;39(3):381–90.
36. Siekmans K, Roche ML, Kung'u JK, Desrochers RE, De-Regil LM. Barriers and enablers for iron folic acid (IFA) supplementation in pregnant women. Matern Child Nutr 2018;14(Suppl 5):e12532.
37. Fernández-Gaxiola A, De-Regil L. Intermittent iron supplementation for reducing anaemia and its associated impairments in menstruating women. Cochrane Database Syst Rev 2011(7):CD009218.
38. Hao L, Yang Q-H, Li Z, Bailey LB, Zhu J-H, Hu DJ, Zhang B-L, Erickson JD, Zhang L, Gindler J, et al. Folate status and homocysteine response to folic acid doses and withdrawal among young Chinese women in a large-scale randomized double-blind trial. Am J Clin Nutr 2008;88(2):448–57.
39. Norsworthy B, Skeaff CM, Adank C, Green TJ. Effects of once-a-week or daily folic acid supplementation on red blood cell folate concentrations in women. Eur J Clin Nutr 2004;58(3):548–54.
40. Samson KLI, Loh SP, Khor GL, Mohd Shariff Z, Yelland LN, Leemaqz S, Makrides M, Hutcheon JA, Sulistyoningrum DC, Yu JJ, et al. Effect of once weekly folic acid supplementation on erythrocyte folate concentrations in women to determine potential to prevent neural tube defects: a randomised controlled dose-finding trial in Malaysia. BMJ Open 2020;10(2):e034598.
41. Institute for Public Health. National Health and Morbidity Survey 2015. Vol. II: non-communicable diseases, risk factors & other health problems. Kuala Lumpur (Malaysia): Ministry of Health; 2015. pp. 1–291.

42. World Health Organization. Prevalence of anaemia in women of reproductive age. [Internet]. Geneva (Switzerland): WHO; 2020. [Accessed 2020 Jul 20]. Available from: https://www.who.int/data/gho/data/indicators/indicator-details/GHO/prevalence-of-anaemia-in-women-of-reproductive-age-(-).
43. Khor GL, Duraisamy G, Peng Loh S, Green TJ, Skeaff CM. Dietary and blood folate status of Malaysian women of childbearing age. Asia Pac J Clin Nutr 2006;15(3):341–9.
44. Blencowe H, Kancherla V, Moorthie S, Darlison MW, Modell B. Estimates of global and regional prevalence of neural tube defects for 2015: a systematic analysis. Ann N Y Acad Sci 2018;1414:31–46.
45. Boo NY, Cheah IGS, Thong MK. Neural tube defects in Malaysia: data from the Malaysian National Neonatal Registry. J Trop Pediatr 2013;59(5):338–42.
46. Green TJ, Skeaff CM, Venn BJ, Rockell JE, Todd JM, Khor GL, Loh SP, Duraisamy G, Muslimatun S, Agustina R, et al. Red cell folate and predicted neural tube defect rate in three Asian cities. Asia Pac J Clin Nutr 2007;16(2):269–73.
47. World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. [Internet]. Geneva (Switzerland): WHO Vitamin and Mineral Nutrition Information System; 2011. [Accessed 2020 Jul 20]. Available from: http://www.who.int/vmnis/indicators/haemoglobin.pdf.
48. Samson KLI, Loh SP, Lee SS, Sulistyoningrum DC, Khoer GK, Mohd Shariff ZB, Ismail IA, Yelland LN, Leemaqz S, Makrides M, et al. 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 2020;5:e003897.
49. Boukerdenna H, Pena-Rosas JP, Garcia-Casal MN. Intermittent iron and folic acid supplementation for prevention of anaemia in menstruating women and adolescent girls. [Internet]. Geneva (Switzerland): World Health Organization, Department of Nutrition for Health and Development, Evidence and Programme Guidance Unit; 2015. [Accessed 2020 Jul 20]. Available from: http://www.who.int/selection_medicines/committees/expert/20/applications/FSFA.pdf.
50. World Health Organization. National Medicines List/Formulary/Standard Treatment Guidelines. Essential medicines selection. Geneva (Switzerland): WHO; 2018.
51. UNICEF. Supply catalogue: iron 60mg+folic ac. 2800mcg tabs/PAC-100[Internet]. New York: UNICEF; 2019. [Accessed 2020 Jul 20]. Available from: https://supply.unicef.org/s1550009.html.