

# THE EFFECT OF ONCE-WEEKLY FOLIC ACID SUPPLEMENTATION ON RED BLOOD CELL FOLATE CONCENTRATIONS IN WOMEN TO DETERMINE THE POTENTIAL TO PREVENT NEURAL TUBE DEFECTS

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## INTRODUCTION

- The WHO recommends weekly iron-folic acid (IFA) supplements for all menstruating women to prevent anemia in countries where the prevalence is >20%.
- Anemia caused by folate deficiency is low worldwide.
- Yet, including folic acid might reduce the risk of a neural tube defect (NTD) should a woman become pregnant.
- There was a lack of evidence that this once weekly 2.8 mg dose would prevent NTDs.

## OBJECTIVES

- 1) To investigate the effect of two doses of folic acid, compared with placebo, on red blood cell (RBC) folate, a biomarker of NTD risk.
- 2) To examine the percentage of women by treatment group who achieved an RBC folate >748 nmol/L, the concentration associated with a low risk of NTDs.

## METHODS

- Three-arm double-blind efficacy trial in Malaysia.
- Non-pregnant women (n=331) were randomised to receive 60 mg iron and either 0, 0.4, or 2.8 mg folic acid once weekly for 16 weeks.
- Fasting venous blood was collected at baseline and 16 weeks and blood folate concentration was determined via microbiological assay.

## RESULTS

Overall, the median (IQR) age of the participants was 18 (18,18) years and 89% of participants were Malay (n=295). At baseline, 18% were anemic and only 5% were folate sufficient. Overall, baseline plasma folate was  $10.7 \pm 5.1$  nmol/L and RBC folate was  $482 \pm 148$  nmol/L.

**Table 1.** Unadjusted mean RBC folate concentrations at baseline and 16 weeks.

	0 mg	0.4 mg	2.8 mg
	n=110	n=110	n=111
<b>Baseline</b>	466 ± 136	474 ± 136	507 ± 168
<b>16 weeks</b>	466 ± 158	554 ± 146	851 ± 208

## DISCUSSION

- Weekly IFA supplements containing 2.8 mg folic acid increase RBC folate more than those containing 0.4 mg.
- 0.4 mg folic acid has minimal impact, it was not more likely than 0 mg to achieve RBC folate >748 nmol/L.
- Increased availability and access to the 2.8 mg formulation is needed.

**2.8 mg folic acid weekly is more effective than the current practice of 0.4 mg weekly at reducing the risk of neural tube defects:**

**4x**

Increases RBC folate 4x as much

**68%**

68% (vs 8%) achieved optimal RBC folate levels

**7x**

7x more likely to achieve a reduced risk of NTD

## GLOBAL HEALTH IMPLICATIONS

Here, we provide the first evidence that the recommended weekly dose of 2.8 mg folic acid, rather than the commonly used 0.4 mg weekly dose, is more effective at increasing RBC folate. This evidence will directly inform WHO guidelines for the use of the weekly 2.8 mg folic acid dose to reduce the risk of NTDs and provides a rationale for the inclusion of this formulation of IFA to the WHO Essential Medicines List in order to accelerate anemia and NTD reduction globally.

## SUPPORTING DATA

**Table 2.** Adjusted mean difference in RBC folate concentrations at 16 weeks.

	Mean Difference (95% CI)	P-value
<b>2.8 vs 0 mg</b>	355 (316 to 394)	<0.0001
<b>0.4 vs 0 mg</b>	84 (54 to 113)	<0.0001
<b>2.8 vs 0.4 mg</b>	271 (234 to 309)	<0.0001

**Table 3.** Relative risk of RBC folate >748 nmol/L at 16 weeks.

	Relative Risk (95% CI)	P-value
<b>2.8 vs 0 mg</b>	16.0 (6.1 to 42.3)	<0.0001
<b>0.4 vs 0 mg</b>	2.2 (0.7 to 6.8)	0.17
<b>2.8 vs 0.4 mg</b>	7.3 (3.9 to 13.7)	<0.0001

## PARTNERS



## FULL ARTICLE

