Antenatal iron supplementation, malaria and pregnancy outcomes: a randomised trial in Kenya

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Mount Etna erupts, 3 December 2015

Acknowledgments

Martin Mwangi and other co-authors

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Iron deficiency in pregnancy

- Antenatal iron supplementation leads to increased haemoglobin concentrations and reduced risk of anaemia at term
- Iron deficiency is associated with severe anemia and maternal death, but causal evidence from randomized trials inconclusive

  What does that mean for maternal and child health?
- Coverage of antenatal iron supplementation is abysmally low in most developing countries

‘The Pemba study’

- Randomised trial, children aged 1-35 months in Pemba, Zanzibar
- Daily oral supplementation with iron and folic acid increased all-cause mortality and hospital admission (combined endpoint) by 12%
- WHO: children in settings with high prevalence of malaria and other infectious diseases should not receive universal iron supplementation

Sazawal et al. Lancet 2006;367:133-43.

Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomised, placebo-controlled trial

Sunil Sazawal, Robert E Black, Mahdi Ramsan, Hababu M Chwaya, Rebecca J Stoltzfus, Arup Dutta, Usha Dhingra, Ibrahim Kabole, Saikat Deb, Mashavi K Othman, Fatma M Kabole

Summary

Background Anaemia caused by iron deficiency is common in children younger than age 5 years in eastern Africa. However, there is concern that universal supplementation of children with iron and folic acid in areas of high malaria transmission might be harmful.

Methods We did a randomised, placebo-controlled trial, of children aged 1–35 months and living in Pemba, Zanzibar. We assigned children to daily oral supplementation with: iron (12·5 mg) and folic acid (50 μg; n=7950), iron, folic acid, and zinc (n=8120), or placebo (n=8006); children aged 1–11 months received half the dose. Our primary endpoints were all-cause mortality and admission to hospital. Analyses were by intention to treat. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN59549825.

Findings The iron and folic acid-containing groups of the trial were stopped early on Aug 19, 2003, on the recommendation of the data and safety monitoring board. To this date, 24 076 children contributed a follow-up of 25 524 child-years. Those who received iron and folic acid with or without zinc were 12% (95% CI 2–23, p=0·02) more likely to die or need treatment in hospital for an adverse event and 11% (1–23%, p=0·03) more likely to be admitted to hospital; there were also 15% (−7 to 41, p=0·19) more deaths in these groups.

Interpretation Routine supplementation with iron and folic acid in preschool children in a population with high rates of malaria can result in an increased risk of severe illness and death. In the presence of an active programme to detect and treat malaria and other infections, iron-deficient and anaemic children can benefit from supplementation. However, supplementation of those who are not iron deficient might be harmful. As such, current guidelines for universal supplementation with iron and folic acid should be revised.

Lancet 2006; 367: 133–43

See Comment page 90

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Introduction

About three-quarters of children younger than age 5 years who live in east Africa are anaemic (haemoglobin concentration <110 g/L; 1·71 μmol/L);[1] much of this anaemia can be ascribed to iron deficiency. International guidelines[2] recommend supplementation with iron and folic acid in children younger than age 2 years in areas with a high prevalence of anaemia. This recommendation is controversial though, particularly in areas affected by admission to hospital or death. Our aim, therefore, was to assess the effect of iron and folic acid supplementation on severe morbidity and mortality.

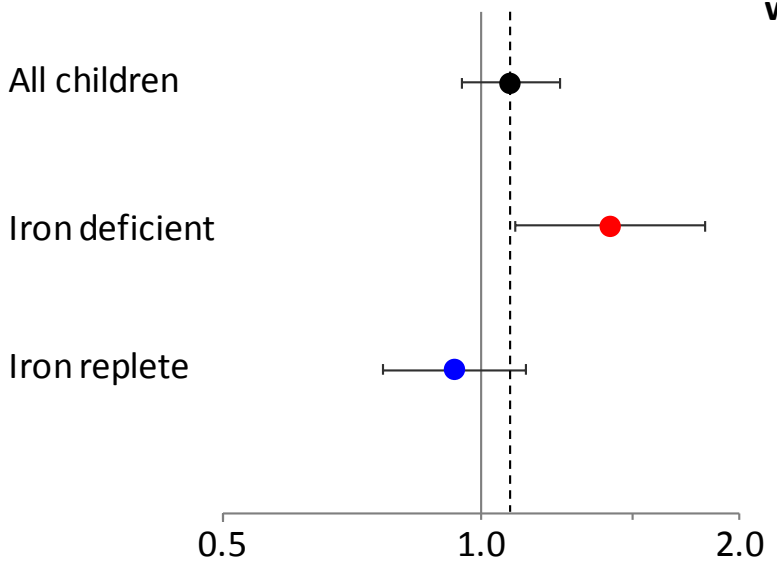
Methods

Participants

Between Jan 1, 2002, and Aug 19, 2003, we did a randomised, double-masked, placebo-controlled trial on Pemba, the smaller of the two islands of the Zanzibar

Supplementation with iron-containing micronutrients and malaria rates, by iron status

Randomised trial, Tanzanian children aged 6-60 months



	No of episodes with vs without micronutrients			Δ Hazard ratio (95% CI)	
All children	816	*vs*	756	8% (–5% to 23%)	
Iron deficient	212	*vs*	141	41% (9% to 82%)	p=0.01
Iron replete	375	*vs*	412	–7% (–23% to 13%)	

Veenemans et al. PLoS Med 2011;8:e1001125.

Iron and malaria risk in pregnancy

- Potential effects of iron interventions on malaria are likely to be most pronounced in pregnancy, when iron absorption is very high
- Observational studies: iron deficiency is associated with a reduced prevalence and density of *Plasmodium* parasites in placental blood
- *Plasmodium* infection in pregnancy: usually asymptomatic, but associated with adverse outcomes:
  - **Infants:** reduced birth weight, intrauterine growth retardation, preterm delivery, increased neonatal mortality
  - **Women:** increased risk of severe anemia and death

Objectives

Primary objective:

1. To assess the effect of daily antenatal iron supplementation (60mg elemental iron as ferrous fumarate) on *Plasmodium* infection risk at delivery

Preplanned secondary objectives:

2. To assess intervention effects on gestational age at delivery, newborn size, and maternal and neonatal iron status at 1 month postpartum
3. To assess effect modification by baseline iron status, gravidity, age and HIV infection

Study population

Inclusion criteria:

- Women aged 15–45 years
- Gestational age 13–23 weeks
- Written informed consent obtained
- Planning to deliver in pre-designated health facility
- Likely available for the duration of intervention

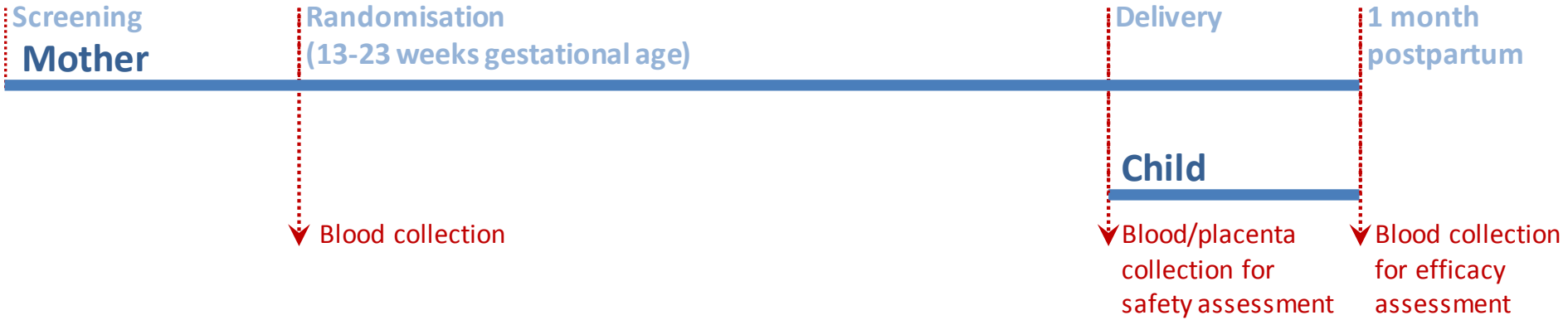
Exclusion criteria:

- Carrying multiples
- No venous blood sample collected
- Haemoglobin concentration < 90 g/L
- Homestead members did not consent
- Obvious intellectual disability
- Metabolic disorder (e.g. diabetes)
- Medical history of sickle cell anaemia, epilepsy
- Obstetric history suggestive of (pre-)eclampsia

Design features

Interventions:

- Supervised daily supplementation from enrolment to 1 month postpartum
- Either 60 mg iron as ferrous fumarate or placebo
- Blinding maintained by use of opaque, colour-coded capsules



Primary outcome:

Any evidence of maternal *Plasmodium* infection at birth, based on:

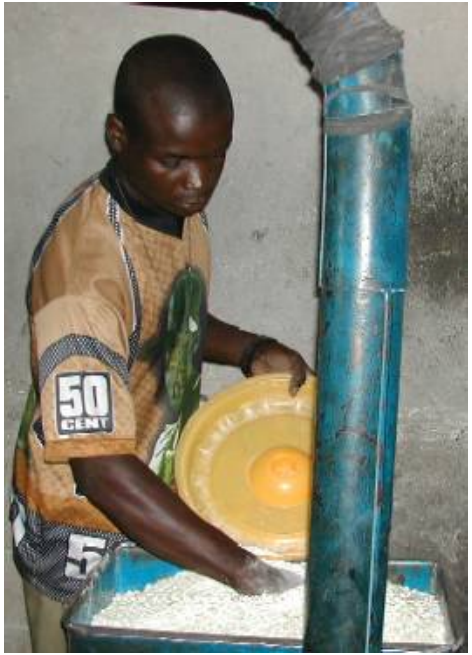
- Rapid antigen tests (pLDH and HRP2), or:
- *P. falciparum* DNA by PCR, or:
- Placental histopathology

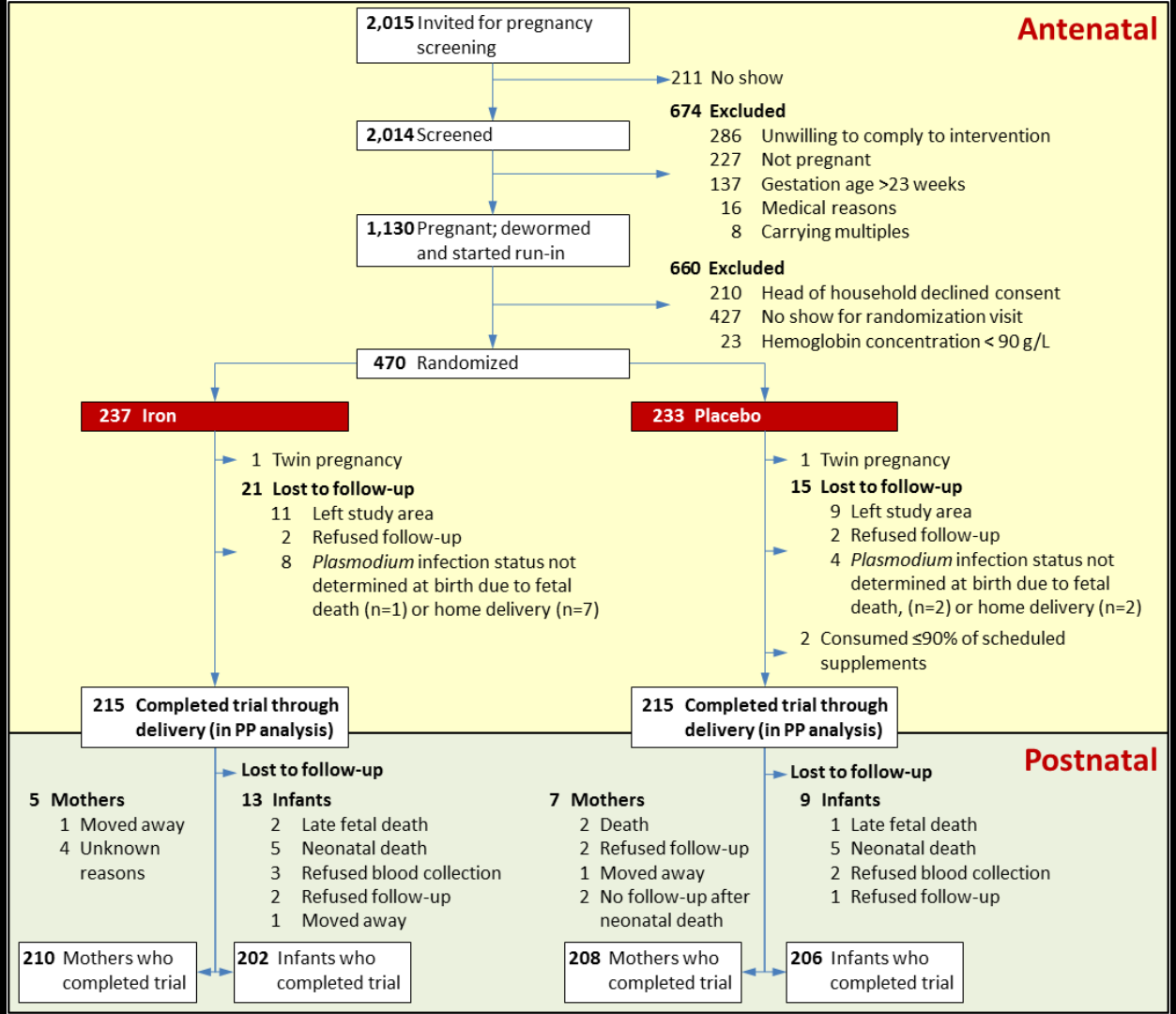
Co-interventions (applied to all study participants)

- Between screening and 1 month postpartum:
  Fortification of flour, supplying 5.6mg elemental iron as NaFeEDTA per day to participating women (weighed food intake studies, 72 pregnant women)

- Before randomization:
  Chemoprevention of helminth infection
  - Praziquantel (3×20mg/kg, 1-day treatment)
  - Albendazole (400mg, single dose)

- During intervention:
  Referral to regular health services for routine antenatal and medical care, including intermittent preventive treatment with sulfadoxine-pyrimethamine against malaria and (as required) antiretroviral therapy




Antenatal
2,015 Invited for pregnancy screening
211 No show
674 Excluded
286 Unwilling to comply to intervention
227 Not pregnant
137 Gestation age >23 weeks
16 Medical reasons
8 Carrying multiples
2,014 Screened
1,130 Pregnant; dewormed and started run-in
660 Excluded
210 Head of household declined consent
427 No show for randomization visit
23 Hemoglobin concentration < 90 g/L
470 Randomized
237 Iron
233 Placebo
1 Twin pregnancy
21 Lost to follow-up
11 Left study area
2 Refused follow-up
8 Plasmodium infection status not determined at birth due to fetal death (n=1) or home delivery (n=7)
1 Twin pregnancy
15 Lost to follow-up
9 Left study area
2 Refused follow-up
4 Plasmodium infection status not determined at birth due to fetal death, (n=2) or home delivery (n=2)
2 Consumed ≤90% of scheduled supplements
215 Completed trial through delivery (in PP analysis)
215 Completed trial through delivery (in PP analysis)
Postnatal
Lost to follow-up
5 Mothers
1 Moved away
4 Unknown reasons
13 Infants
2 Late fetal death
5 Neonatal death
3 Refused blood collection
2 Refused follow-up
1 Moved away
Lost to follow-up
7 Mothers
2 Death
2 Refused follow-up
1 Moved away
2 No follow-up after neonatal death
9 Infants
1 Late fetal death
5 Neonatal death
2 Refused blood collection
1 Refused follow-up
210 Mothers who completed trial
202 Infants who completed trial
208 Mothers who completed trial
206 Infants who completed trial

Serious adverse events

Maternal events

Adverse events	Iron	Placebo
Death	0	2
Hospital admission	1	4
Eclampsia	0	1
Atonic uterine contraction	0	1
General sickness	4	3
Malaria	1	1
Pneumonia	1	0
Meningitis	1	0
Breech delivery	1	0
Total	**9**	**12**

Fetal and neonatal events

Adverse events	Iron	Placebo
Fetal death	3	3
Neonatal death	4	4
Infant death after 28 days of life	1	1
Neural tube defect	0	2
Neonatal sepsis	1	1
Total	**9**	**11**

Effect of iron supplementation on selected outcomes **at birth**

Indicator	Iron	Placebo	Difference (95% CI)	P-value
Maternal outcomes				
***Plasmodium* infection**	**50.9%**	**52.5%**	**–1.2% (–11.8% to 9.5%)**	**0.83**
Haemoglobin concentration, g/L	120.8	111.5	9.3 (5.9 to 12.6)	<0.001
Anaemia (Hb concentration <110 g/L)	22.0%	50.4%	–28.4% (–36.9% to –19.8%)	<0.001
Erythrocyte ZPP-haem ratio, µmol/mol	29.9 [a]	66.9 [a]	–55.3% (–62.5% to –46.7%)	<0.001
Neonatal outcomes				
Birth weight, g	3,202	3,053	150 (56 to 244)	0.002
Low birth weight (<2,500 g)	4.3%	10.3%	–6.0% (–11.1% to –0.8%)	0.02
Gestational age at delivery, days	274.4	271.0	3.4 (0.8 to 5.9)	0.009
Premature birth (< 37 weeks gestation)	9.1%	16.2%	–7.1% (–13.2% to –1.1%)	0.02
Birthweight for gestational age z-score, SD	0.52	0.31	0.21 (–0.11 to 0.52)	0.20
Length, cm	50.6	49.7	0.9 (–0.1 to 1.8)	0.07
Head circumference, cm	34.9	34.6	0.3 (–0.2 to 0.8)	0.28

Values indicate group mean or [a] geometric mean unless indicated otherwise

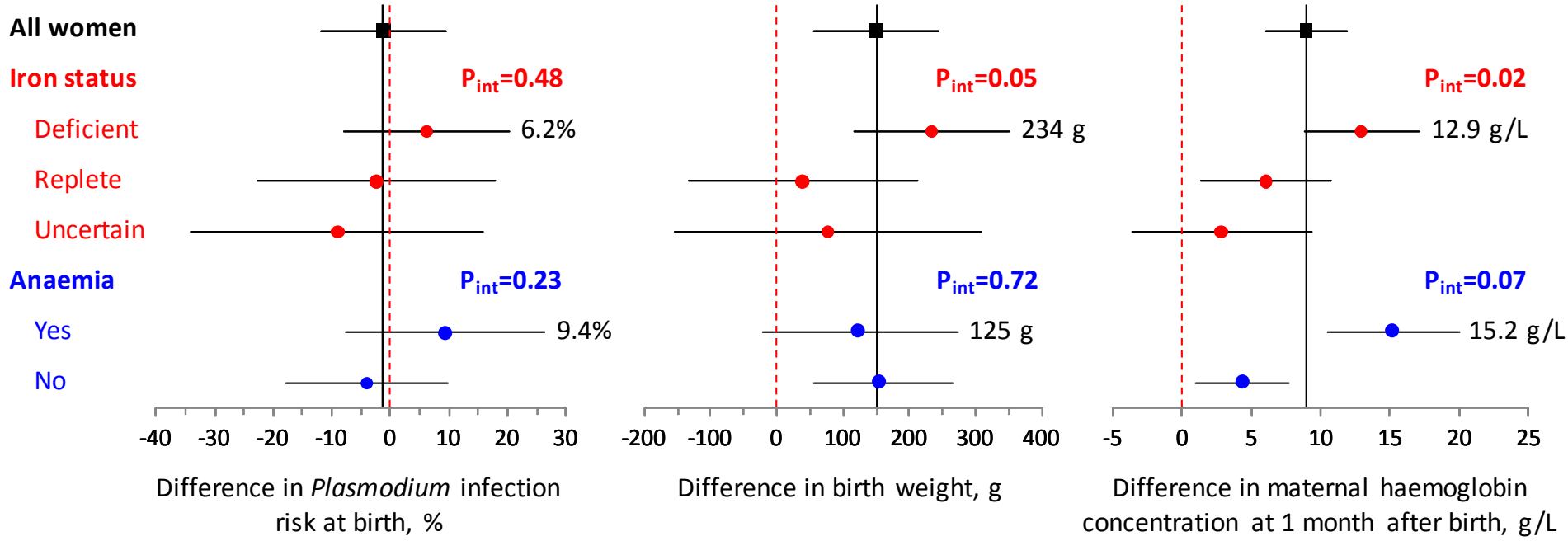
Effect of iron supplementation on selected outcomes **at 1 month after birth**

Indicator	Iron	Placebo	Difference (95% CI)	P-value
Maternal outcomes				
Haemoglobin concentration, g/L	128.9	119.9	9.0 (6.1 to 11.9)	<0.001
Anaemia (Hb concentration <120 g/L)	43.2%	65.7%	–22.4% (–31.4% to –13.5%)	<0.001
Plasma ferritin concentration, µg/L	32.1 [a]	14.4 [a]	123% (86% to 169%)	<0.001
Iron deficiency (ferritin concentration <15µg/L)				
All women	19.8%	56.0%	–36.2% (–44.9% to –27.5%)	<0.001
Those without inflammation [b]	21.1%	59.5%	–38.5% (–49.7% to –27.3%)	<0.001
Plasma transferrin concentration, g/L	2.67	3.07	–0.40 (–0.49 to –0.30)	<0.001
Plasma transferrin receptor concentration, mg/L	1.81 [a]	2.53 [a]	–28.6% (–35.5% to –21.0%)	<0.001
Erythrocyte ZPP-haem ratio, µmol/mol	31.9 [a]	74.5 [a]	–52.7% (–64.0% to –49.1%)	<0.001
Neonatal outcomes				
Haemoglobin concentration, g/L	134.5	133.2	1.3 (–5.2 to 7.8)	0.69
Plasma ferritin concentration, µg/L	163.0 [a]	138.7 [a]	17.5% (2.4% to 34.8%)	0.02
Plasma transferrin receptor concentration, mg/L	1.21 [a]	1.27 [a]	–4.4% (–11.3% to 2.9%)	0.23

Values indicate group mean or [a] geometric mean unless indicated otherwise

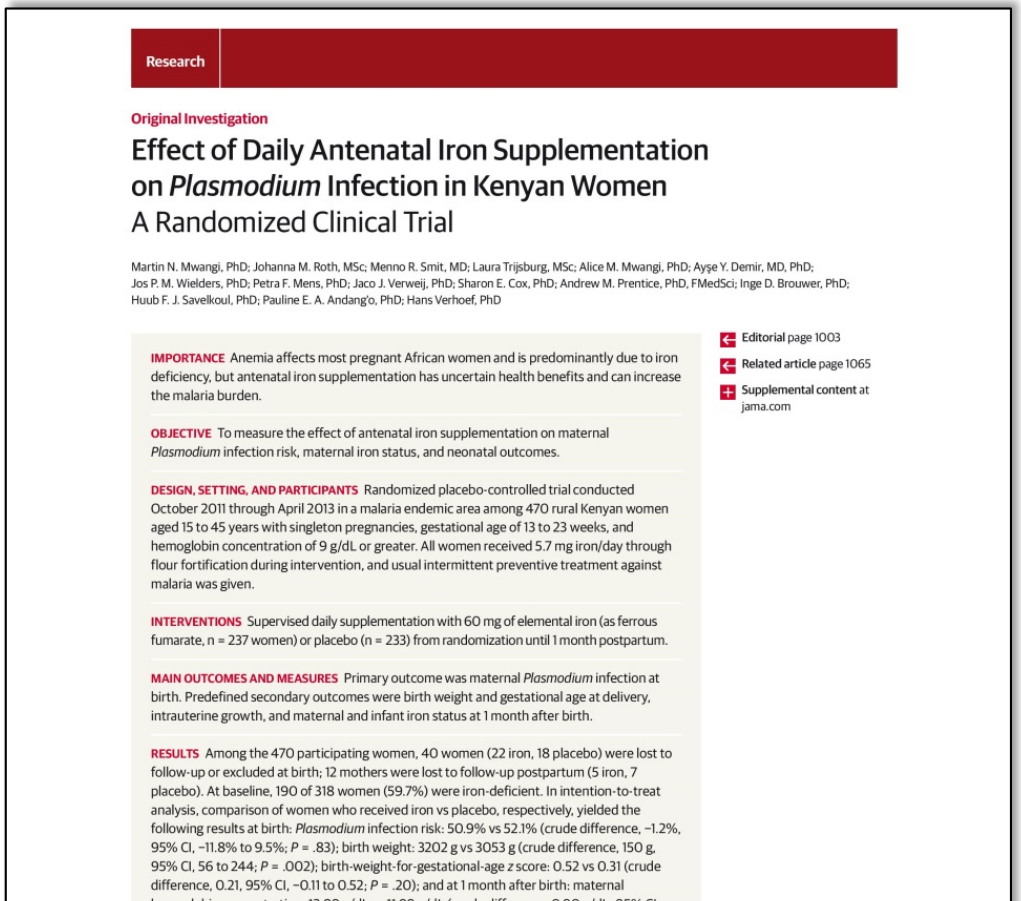
[b] Concentrations of C-reactive protein < 10 mg/L and α_1-acid glycoprotein < 1.0 g/L

Effect of iron supplementation on selected outcomes, by subgroup



Horizontal bars indicate 95% CIs

Kenya trial (Mwangi et al. JAMA 2015): key findings



Research

Original Investigation

Effect of Daily Antenatal Iron Supplementation on *Plasmodium* Infection in Kenyan Women
A Randomized Clinical Trial

Martin N. Mwangi, PhD; Johanna M. Roth, MSc; Menno R. Smit, MD; Laura Trijsburg, MSc; Alice M. Mwangi, PhD; Ayşe Y. Demir, MD, PhD; Jos P. M. Wielders, PhD; Petra F. Mens, PhD; Jaco J. Verweij, PhD; Sharon E. Cox, PhD; Andrew M. Prentice, PhD, FMedSci; Inge D. Brouwer, PhD; Huub F. J. Savelkoul, PhD; Pauline E. A. Andang'o, PhD; Hans Verhoef, PhD

Editorial page 1003
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IMPORTANCE Anemia affects most pregnant African women and is predominantly due to iron deficiency, but antenatal iron supplementation has uncertain health benefits and can increase the malaria burden.

OBJECTIVE To measure the effect of antenatal iron supplementation on maternal *Plasmodium* infection risk, maternal iron status, and neonatal outcomes.

DESIGN, SETTING, AND PARTICIPANTS Randomized placebo-controlled trial conducted October 2011 through April 2013 in a malaria endemic area among 470 rural Kenyan women aged 15 to 45 years with singleton pregnancies, gestational age of 13 to 23 weeks, and hemoglobin concentration of 9 g/dL or greater. All women received 5.7 mg iron/day through flour fortification during intervention, and usual intermittent preventive treatment against malaria was given.

INTERVENTIONS Supervised daily supplementation with 60 mg of elemental iron (as ferrous fumarate, n = 237 women) or placebo (n = 233) from randomization until 1 month postpartum.

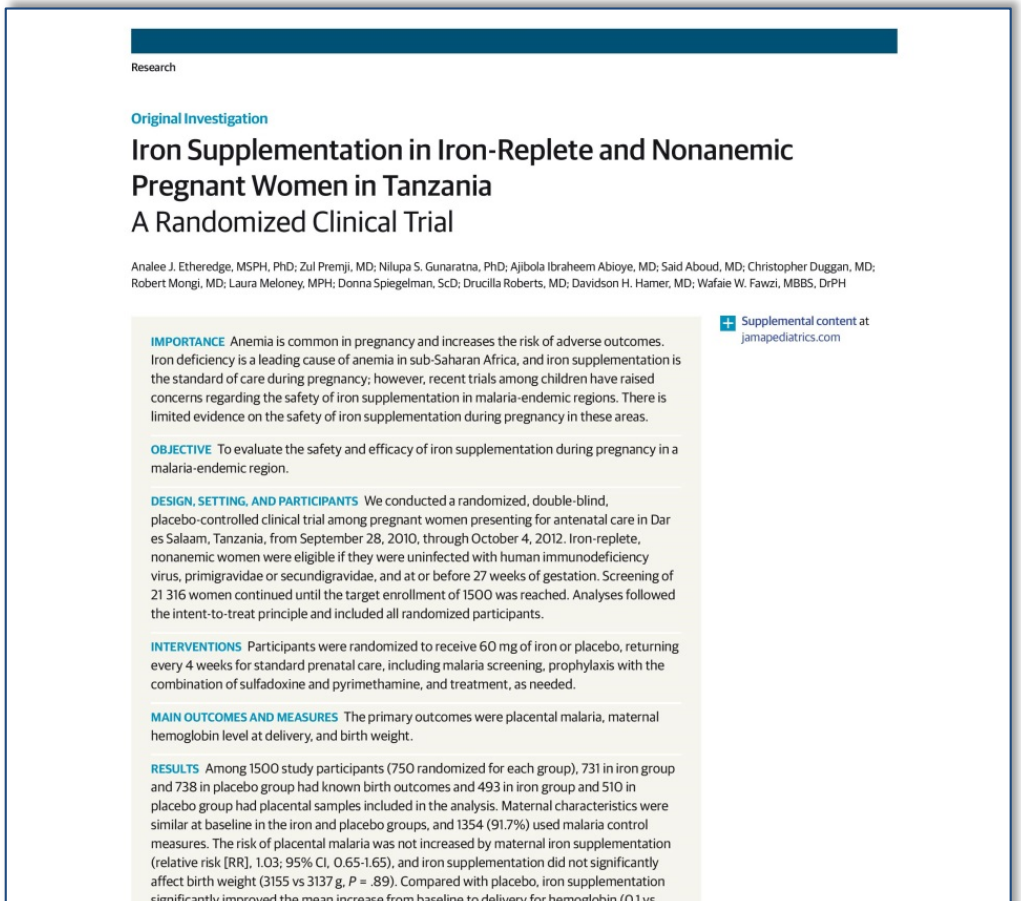
MAIN OUTCOMES AND MEASURES Primary outcome was maternal *Plasmodium* infection at birth. Predefined secondary outcomes were birth weight and gestational age at delivery, intrauterine growth, and maternal and infant iron status at 1 month after birth.

RESULTS Among the 470 participating women, 40 women (22 iron, 18 placebo) were lost to follow-up or excluded at birth; 12 mothers were lost to follow-up postpartum (5 iron, 7 placebo). At baseline, 190 of 318 women (59.7%) were iron-deficient. In intention-to-treat analysis, comparison of women who received iron vs placebo, respectively, yielded the following results at birth: *Plasmodium* infection risk: 50.9% vs 52.1% (crude difference, −1.2%, 95% CI, −11.8% to 9.5%; $P = .83$); birth weight: 3202 g vs 3053 g (crude difference, 150 g, 95% CI, 56 to 244; $P = .002$); birth-weight-for-gestational-age z score: 0.52 vs 0.31 (crude difference, 0.21, 95% CI, −0.11 to 0.52; $P = .20$); and at 1 month after birth: maternal

Effects of antenatal iron supplementation:

1. No evidence that it affects malaria risk
2. Birth weight increased by 150g; risk of low birth weight decreased by 58%
3. In women with initial iron deficiency: birth weight increased by 234g
4. Gestational duration and neonatal length increased
5. Risk of premature birth decreased
6. Maternal haemoglobin concentration at birth increased at birth and at 1 month after birth
7. Maternal and infant iron stores at 1 month after birth enhanced
8. No evidence that effect is modified by IPT use

Tanzania trial (Etheredge et al. JAMA Pediatr 2015): key findings



Research

Original Investigation

Iron Supplementation in Iron-Replete and Nonanemic Pregnant Women in Tanzania

A Randomized Clinical Trial

Analee J. Etheredge, MSPH, PhD; Zul Premji, MD; Nilupa S. Gunaratna, PhD; Ajibola Ibraheem Abioye, MD; Said Aboud, MD; Christopher Duggan, MD; Robert Mongi, MD; Laura Meloney, MPH; Donna Spiegelman, ScD; Drucilla Roberts, MD; Davidson H. Hamer, MD; Wafaie W. Fawzi, MBBS, DrPH

Supplemental content at jamapediatrics.com

IMPORTANCE Anemia is common in pregnancy and increases the risk of adverse outcomes. Iron deficiency is a leading cause of anemia in sub-Saharan Africa, and iron supplementation is the standard of care during pregnancy; however, recent trials among children have raised concerns regarding the safety of iron supplementation in malaria-endemic regions. There is limited evidence on the safety of iron supplementation during pregnancy in these areas.

OBJECTIVE To evaluate the safety and efficacy of iron supplementation during pregnancy in a malaria-endemic region.

DESIGN, SETTING, AND PARTICIPANTS We conducted a randomized, double-blind, placebo-controlled clinical trial among pregnant women presenting for antenatal care in Dar es Salaam, Tanzania, from September 28, 2010, through October 4, 2012. Iron-replete, nonanemic women were eligible if they were uninfected with human immunodeficiency virus, primigravidae or secundigravidae, and at or before 27 weeks of gestation. Screening of 21 316 women continued until the target enrollment of 1500 was reached. Analyses followed the intent-to-treat principle and included all randomized participants.

INTERVENTIONS Participants were randomized to receive 60 mg of iron or placebo, returning every 4 weeks for standard prenatal care, including malaria screening, prophylaxis with the combination of sulfadoxine and pyrimethamine, and treatment, as needed.

MAIN OUTCOMES AND MEASURES The primary outcomes were placental malaria, maternal hemoglobin level at delivery, and birth weight.

RESULTS Among 1500 study participants (750 randomized for each group), 731 in iron group and 738 in placebo group had known birth outcomes and 493 in iron group and 510 in placebo group had placental samples included in the analysis. Maternal characteristics were similar at baseline in the iron and placebo groups, and 1354 (91.7%) used malaria control measures. The risk of placental malaria was not increased by maternal iron supplementation (relative risk [RR], 1.03; 95% CI, 0.65-1.65), and iron supplementation did not significantly affect birth weight (3155 vs 3137 g, $P = .89$). Compared with placebo, iron supplementation

Effects of antenatal iron supplementation:

1. No evidence that antenatal iron supplementation affects risk of malaria, birth weight or risk of premature birth

2. Haemoglobin concentration at birth increased by 9g/L ($p<0.001$); ferritin concentration increased by 38µg/L ($p<0.001$)

Kenya trial *vs* Tanzania trial: comparison of selected issues in design and results

	Kenya (Mwangi et al. JAMA 2015)	Tanzania (Etheridge et al. JAMA Pediatr 2015)
n	470	1,500
Study population	Rural, poor	Urban
Malaria transmission	High	Low
SP chemoprevention	As per routine care	Monthly administered
Has insecticide-treated net	15.2% iron; 15.9% placebo	88.5% iron; 88.9% placebo
Iron-deficient, anaemic women	Included	Excluded
HIV-infected women	Included	Excluded
Blinding	Capsules	Tablets (do not mask iron taste)
Adherence assessment	Swallowing of supplements daily observed	Monthly tablet counts
***Plasmodium* infection at birth**	50.9% iron; 52.1% placebo	6.7% iron; 6.5% placebo
Effect of iron on *Plasmodium* risk	–1.2% (95%CI: –11.8% to 9.5%)	0.2% (RR: 3%, 95%CI: –35% to 65%; p=0.89)
Effect on birth weight	150g (56g to 244g; p=0.002)	26g (p=0.89)
Preterm birth (<37 weeks)	9.1% vs 16.2%	15.0% vs 16.5%
Effect on preterm birth risk	–7.1% (95%CI: –13.2% to –1.1%; p=0.02)	–1.5% [RR: –9%, 95%CI: –29% to 17%, p=0.46)

Kenya trial (Mwangi et al. 2015) *vs* Tanzania trial (Etheridge et al. 2015)

Kenya trial	Tanzania trial
In primary analysis, upper limit of 95% CI of the effect of iron excludes an increase in the risk of *Plasmodium* infection beyond 9.5%	Corresponding value: 65% (the 95% CI is much wider because of low risk of *Plasmodium* infection)
Results apply to more heterogenous population including pregnant women with anaemia, iron deficiency, HIV infection, and with low coverage of interventions against malaria (IPT, ITNs)	Results cannot be extrapolated to women with these conditions or with low coverage of interventions against malaria (because they were excluded)
Effect on birth weight was large because women with iron deficiency and anaemia were retained in the trial	Effect on birth weight was small because women with iron deficiency and anaemia were excluded

"There was no evidence that gains in birth weight depended on gravidity, maternal age, HIV infection, anemia, and IPT use, suggesting benefits from iron for all subgroups thus defined, including primigravidae and those who did not receive IPT. Thus, our results may apply to pregnant women in other low- and middle-income countries, although the effect on birth weight can vary depending on the prevalence of iron deficiency." – Mwangi et al. 2015

Policy implications

- In our study:
  - 60% of women were iron deficient
  - Correction of iron deficiency increased birth weight by 234g
  - Only 16.8 women needed to be supplemented to prevent a single case of low birth weight
- Antenatal iron supplementation has potentially immense benefits for infant survival and health that should outweigh any possible concerns about risks of malaria
- Policy makers must give top priority to scaling up and increasing universal coverage of universal iron supplementation in pregnancy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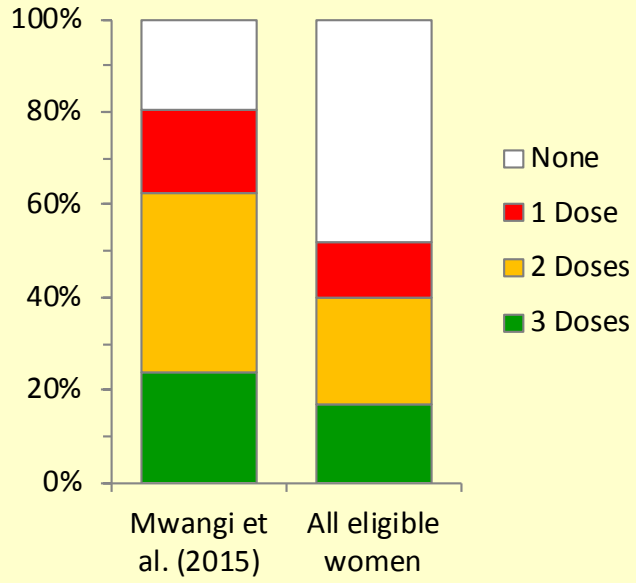
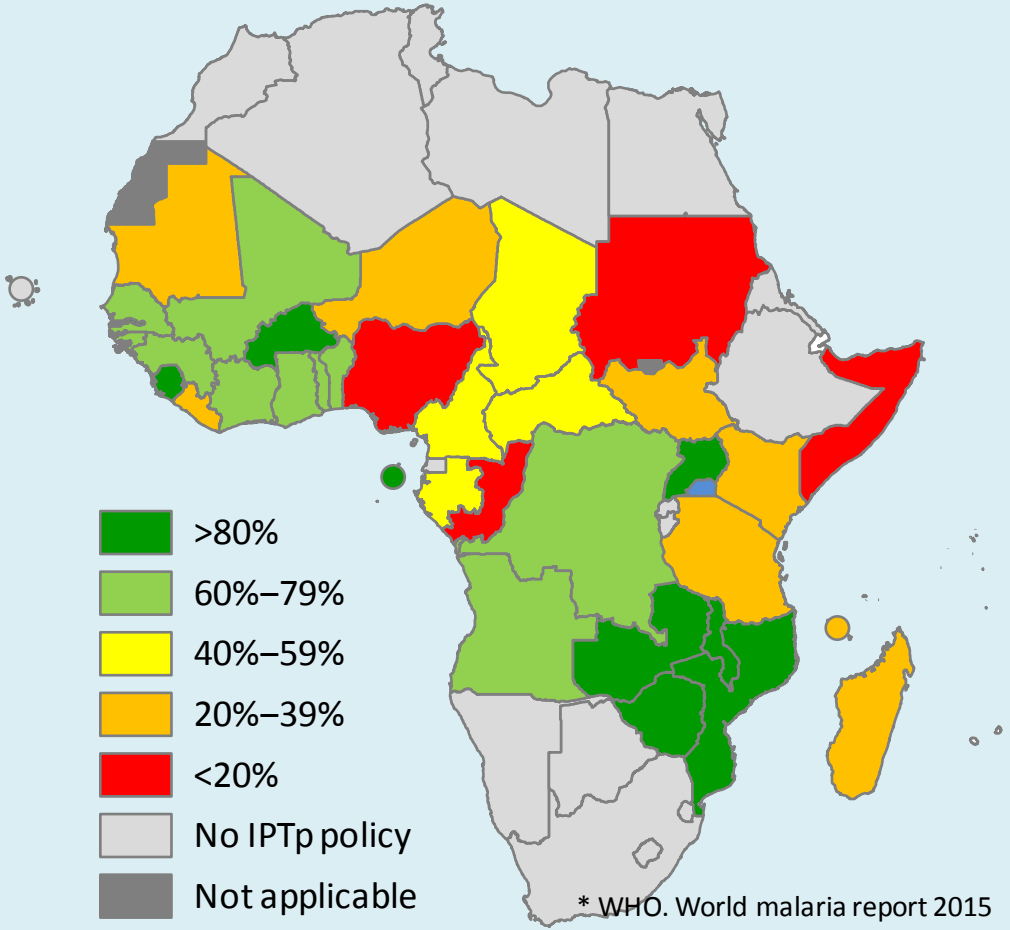
WHO policy update 2014:

IPT_p doses should be delivered at each antenatal care (ANC) visit after the first trimester (the schedule should follow the recommended number of ANC visits), with a minimum of three doses received during each pregnancy

IPT_p coverage (%): Mwangi et al. (2015) versus all eligible women*

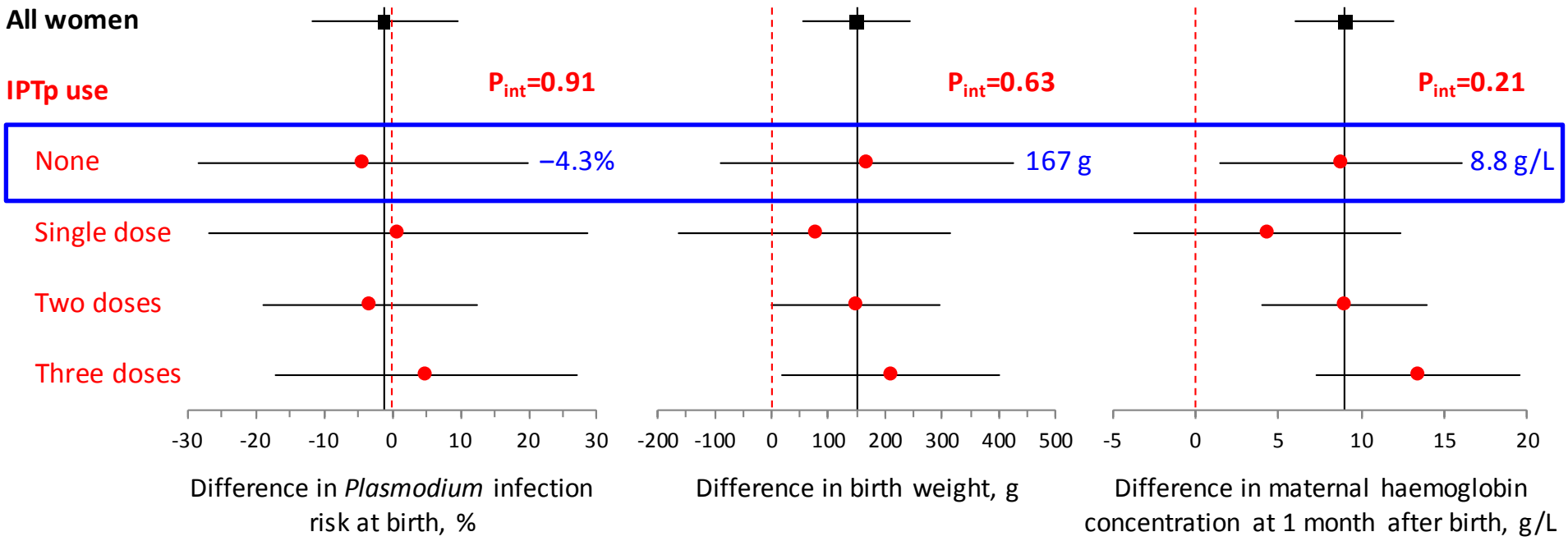


Percentage of pregnant women receiving ≥ 1 dose of IPT_p, 2014*



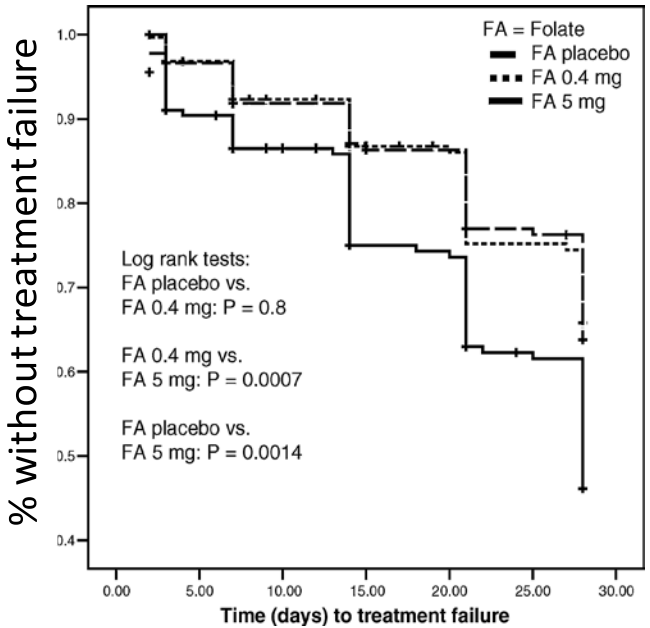
* WHO. World malaria report 2015

Effect of iron supplementation on selected outcomes, influence of IPT use



Horizontal bars indicate 95% CIs

Folic acid supplementation can result in therapeutic failure of sulfadoxine-pyrimethamine against malaria: a randomised trial in Kenyan pregnant women



Intervention group	Hazard ratio (95% CI)
Placebo	Reference
Folic acid, 0.4 mg/day	1.09 (0.58 to 2.04)
Folic acid, 5 mg/day	2.01 (1.15 to 3.51)

Ouma et al. PLoS Clin Trial 2006

Power and sample size calculations: irrelevant and misleading in study interpretation

"The study size was relatively small, and thus the risk of severe adverse effects that occur at low frequency could not be ruled out. The power of the study was sufficient to detect only large differences (i.e., increased infection rate of 35% or more). Loss to follow-up and missing data resulted in further attenuating the sample size." – Christian and Black. [Editorial] JAMA 2015;314:1003-05.

	Kenya trial	Tanzania trial
Sample size calculation	450 women (both groups) needed to detect 35% effect on *Plasmodium* infection risk	1,500 women (both groups) needed to detect 35% effect on *Plasmodium* infection risk
	Assumptions: • Power, (1–β)=92% • α=0.05 • Risk in placebo group: 50% • Loss to follow-up: 5% in the iron group	Assumptions: • Power, (1–β)=80% • α=0.05 • Risk in placebo group: 20% • Loss to follow-up: 10%
Effect	Difference: –1.2% (95%CI: –11.8% to **9.5%**)	RD: 0.2% ; RR: 3% (95%CI: –35% to **65%**)
	Actual values: • Risk in placebo group: 52.1%	Actual values: • Risk in placebo group: 6.5%