# WHO consultation on prevention and control of iron deficiency in infants and young children in malaria endemic areas
# Lyon, France 12-14 June 2006

The consultation was organized to review the results of **two large supplementation trials**, one in **Nepal (low prevalence of malaria)** and the other in **Zanzibar (intense, perennial stable transmission of Plasmodium falciparum)** because **routine supplementation** of **all children under the age of 3 years** resulted in a **12% increase in the likelihood of treatment in hospital or death (95% CI: 1.02-1.23, p = 0.02)** in the **Zanzibar** trial, but **no** significant **difference** in mortality or attack rates for diarrhea, dysentery or respiratory infections in **Nepal**.

# Design of the two trials

Both were placebo controlled supplementation trials in children aged 1-35 months. There were four arms; iron (12.5 mg Fe as $FeSO_4$ ) and folic acid (50ug), iron, folic acid and zinc (10 mg), zinc alone, and control (placebo). Most children were given the supplements between meals in the Zanzibar study. The iron and folic acid containing arms were terminated early and the results reported in January 2006.

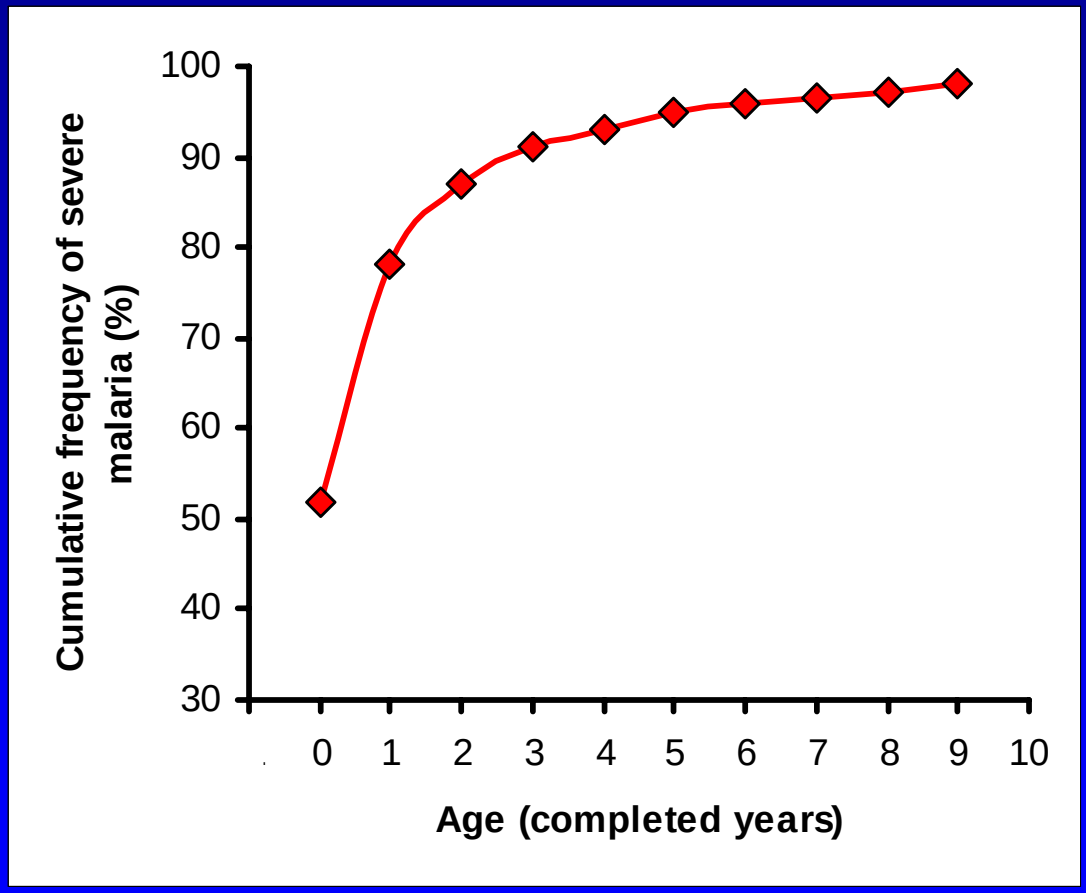
- **Nepal** (n = ~ 8500 / arm)

  Primary outcome measure: all-cause mortality

  Secondary outcome measures included incidence and severity of diarrhea, dysentery and acute respiratory illnesses

  Hemoglobin and serum ferritin measured in a subsample at 12 months (n = ~ 165 / arm); substantial reduction in iron deficiency and anemia in groups receiving iron and folic acid

# Cumulative frequency of severe malaria episodes




English & Snow: Lancet 367:90, 2006

# Design of the two trials

- **Zanzibar** (n = ~ 8000 / arm)

  Primary outcome measure: all-cause mortality and admission to hospital (severe morbidity) - 12% increase

  **Substudy** (n = ~ 2413 total)

  Groups and outcome measures were the same as in the main trial

  Baseline evaluation: physical examination, height, weight, Hb, ZPP/H, malaria smear; children with parasite counts >5000 $mm^{-3}$ and axilliary temp >37.5 $^{o}$ C given sulfadoxine/pyrimethamine

  Results of giving iron and folic acid

  ZPP/H <80 (iron sufficient) severe morbidity RR 1.63 (0.72 - 3.66, p = 0.24)

  ZPP/H ≥80 (iron deficient) severe morbidity RR 0.62 (0.41 - 0.93, p = 0.02)

  Hb > 100 g/L severe morbidity RR 1.08 (0.58 -1.98, p = 0.8)

  Hb 70-100 g/L severe morbidity RR 0.59 (0.37 - 0.92, p = 0.02)

# WHO consultation on iron and malaria

- **Objectives**
  - Review the scientific evidence related to the risks and benefits of giving iron to infants and young children particularly in malaria endemic regions
  - Provide guidance on iron and folic acid supplementation to programs particularly in malaria endemic regions

- **Expertise of participants**
  - Nutrition trials and programs
  - Micronutrient nutrition – iron, vitamin A, zinc, folic acid
  - Iron overload and toxicity
  - Malaria
  - Basic science of iron / pathogen interactions
  - Food chemistry

# Morbidity from iron deficiency in young children

Iron deficiency due to insufficient bioavailable iron in the diet is most prevalent between 4 and 24 months

Iron deficiency at 6-24 months is associated with:

- Lower cognitive and motor development test scores
- Disturbed social-emotional behavior
- Slower neural transmission evoked potentials, altered sleep, poor recognition memory, altered spontaneous motor activity

**Chronic severe iron deficiency** in infants may have **long term consequences** which may **not be reversed by later iron therapy**

# Morbidity from iron deficiency in young children

**Increased risk** of serious adverse events **in iron deficient children** (Zanzibar sub-study – improved access to medical care)

Children with **iron deficiency (ZPP/H ≥80)** were **twice as likely to be admitted to hospital or die** (severe adverse event rates 9.76 and 4.83 / 100 child yrs in the placebo group)

Iron and folic acid **reduced** the risk in **iron deficient children** by 38%

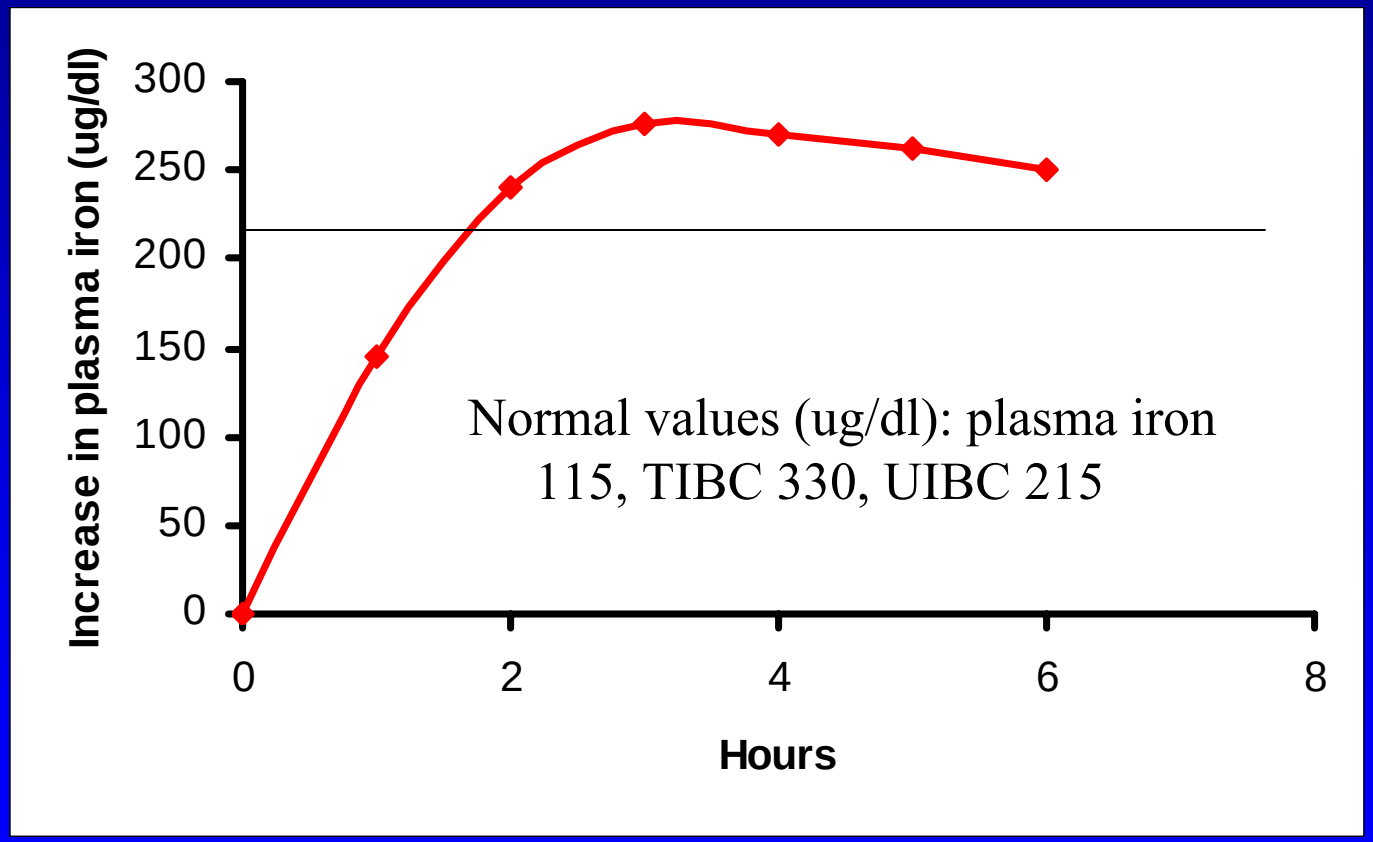
# Pathophysiology of interactions between iron, malaria and infection

- The interactions between malaria parasites, iron status and immune responses is complex; the mechanisms by which iron increases the risk of severe morbidity is unclear
- Folic acid was always given with iron in the Zanzibar study; a role for folic acid in causing increased morbidity cannot be excluded
- The possible influence of the common genetic polymorphisms for globin, G6PD, haptoglobin and transmembrane iron transporters requires further study
- Whether the effects of iron and possibly folic acid supplementation are related only to malaria or apply to other infections such tuberculosis and HIV is unknown

# Pathophysiology of interactions between iron, malaria and infection

- Iron is essential for normal cellular and (to a lesser extent) humoral immunity
- Iron in the human body is normally always tightly bound to a protein (transferrin for transport, ferritin for storage or several transmembrane transporters)
- Oral iron supplements may be absorbed rapidly so that the iron binding capacity of transferrin is exceeded; some of the iron is then bound less tightly – called non-transferrin-bound iron (NTBI)
- All pathogens require iron; NTBI may be more available to pathogens; NTBI may also promote oxidative damage

# Increase in plasma iron after oral iron dose




100 mg Fe as FeSO4 with a bread roll in adults
adapted from Hoppe et al., BJN 92:485, 2004

# Pathophysiology of interactions between iron, malaria and infection - conclusions

- **High ZPP/H values** and, to a lesser extent, **low hemoglobin** values identify children who will **benefit from iron and folic acid supplementation**
- There is currently **no evidence to suggest that iron deficiency is protective against severe malarial morbidity**
- **When iron deficiency is identified, it should be treated**
- Iron supplements given to iron deficient children under the age of 3 years may reduce severe malaria related morbidity by ~ 40% in settings where treatment for malaria is readily available

# Recommendations

- **Non-malarial regions**

  Measures to improve iron status during pregnancy

  Delayed cord clamping

  Exclusive breast feeding for the first 6 months

  Complementary foods high in bioavailable iron

  Supplementation in accordance with the current WHO guidelines (INACG, WHO, UNICEF, 1988, WHO, 2001)

# Recommendations

**Malaria-endemic regions, children under six months**

Ensure optimal iron status during pregnancy

Delayed cord clamping

Exclusive breast feeding

Coordination with malaria prevention and treatment programs

Premature and low birth weight infants: iron supplements for 3 months starting at 2 months (very high likelihood of iron deficiency)

Full term, normal birth weight infants: screening for iron deficiency (laboratory indicators where available; clinical anemia), iron for 3 months starting as early as 2 months in iron deficient infants

No folic acid

# Recommendations

**Malaria endemic regions, children 6 to 24 months**

- Coordination with malaria prevention and treatment programs
- Control of infections and other parasitic diseases
- Breast feeding, nutritionally adequate complementary foods fortified with high bioavailability iron
- Where fortified complementary foods are not available, supplemental iron with food for 3 months only to iron deficient children (laboratory screening where possible, clinical anemia)
- No folic acid

# Recommendations

The recommendations for iron supplements also apply to iron preparations administered through home fortification with powders, crushable tablets and fat-based products (sprinkles, etc)

There are plausible theoretical reasons to suggest that these preparations may be safer than iron supplements, but there is at present no evidence to justify these claims

# Recommendations – research priorities

- **Mechanisms responsible for adverse effects of iron supplementation in malaria-endemic regions**
  - Delivery methods, type of preparation, pharmaco-kinetics of absorption, possible role of NTBI
  - Role of comorbidity due to other infections
  - Role of iron regulatory proteins
- **Assessment of iron status in malaria-endemic regions**
  - Field friendly indicators, ZPP/H
- **Risks/benefits of alternative methods for delivering iron**
  - Home fortification, fortified complementary foods