REVIEW ARTICLE

Risks of Routine Iron and Folic Acid Supplementation for Young Children

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Context: Almost 70% of young children in India are anemic. Current policy recommends routine iron-folic acid (IFA) supplementation to all under 5 children. A potential risk of this approach is an increase in infectious diseases in general, and malaria in particular.

Evidence acquisition: An extensive literature search including PubMed, the World Health Organization (WHO) document library, and the Indian Government database, for documents regarding IFA supplementation in under-5 children.

Results: Previously, systematic reviews had suggested adverse effects of IFA supplementation in malaria endemic settings. However, a recent large trial in Tanzania has found clear evidence of increased mortality, chiefly due to malaria, among children receiving routine IFA, whilst a simultaneous study in Nepal (a non-malarious region) found no adverse effects on morbidity or mortality from infectious disease attributable to IFA. These findings have prompted the World Health Organization to revise recommendations regarding IFA supplementation in malaria endemic areas.

Conclusions: India has a non-homogenous distribution of malaria endemicity. We propose that although no change to IFA supplementation be made in non-malarious regions, routine IFA should be provided in malarious regions once malaria control and primary health care infrastructure are functioning well.

Key Words: *Anemia, Folic Acid, India, Iron, Malaria, Public Health.*

Anemia is an important health problem in India, especially among children. The third National Family Health Survey (NFHS-3) (2005-06) found that the prevalence of anemia among under-5 children approaches 70%(1). Until recently, the World Health Organization guidelines for prevention of anemia recommended that prophylactic iron/ folic acid be administered to all children aged 6-24 months living in communities where the prevalence of anemia in this group is above 40%(2). However, recent evidence has raised concerns about the safety of routine IFA supplementation for young children in regions where malaria transmission is intense and infectious diseases highly prevalent. Malaria and other infections remain important among children in India.

We aim to present and discuss evidence of interactions between IFA supplementation and malaria, and briefly, other prevalent infectious diseases. We will explore the risks and benefits of IFA supplementation for young (under-5) children, in malaria-endemic and malaria non-endemic areas and place these conclusions in the Indian context. Our search strategy for this review employed the following terms, limited to under-5 children: "iron deficiency + malaria", "malaria + India", "anemia + India", as well as a search of WHO and Government of India documents published since 2000 addressing "anemia", "iron deficiency" and "malaria + anemia".

ANEMIA AND MALARIA IN INDIA

The NFHS-2 (1998-99) and NFHS-3 (2005-06) surveys provided comprehensive estimates of

anemia prevalence in India, by measuring capillary blood hemoglobin levels. Among children aged 9-23 months, the prevalence of anemia (haemoglobin <11g/dL) is above 80%. The peak prevalence occurred in children aged 12-17 months (84.5%). Anemia was above 50% in all but four states(1). Of particular concern, the study also found that the prevalence of anemia among children aged 6-35 months appeared to have risen from 74.3% to 78.9% between the NFHS-2 and the survey in 2006(3). The burden of anemia has failed to improve despite improvements in other nutrition parameters, specifically stunting and underweight, in a climate of broader national economic growth(4).

Despite the high prevalence of anemia among children in India, very little is known about the etiology. Although there are reasons to believe that the anemia is chiefly due to iron deficiency [largely vegetarian diets, high consumption of cereals containing inhibitors of iron absorption(5), endemic intestinal parasite infection(6)], some studies have also revealed deficiencies in other haematinic micronutrients, for example vitamin A(7) and B_{12}(8). Few studies using laboratory measurements explore micronutrient deficiencies in rural Indian children(9).

The National Nutritional Anemia Control Programme (NNACP) recommends routine supplementation with iron (20mg) and folic acid (100mcg) to all children aged 6-60 months, for 100 days per year regardless of anemia status(10,11).

BENEFITS OF IRON SUPPLEMENTATION

Randomized controlled trials evaluating influences of iron supplementation on mental, motor and physical development and hemoglobin response in children have been systematically reviewed. A beneficial effect from iron supplementation on either mental or motor development or physical growth among young children could not be identified, although where baseline iron deficiency anaemia was prevalent, iron supplementation appears to benefit mental development(12). There is also some data to suggest impairment in linear growth in developed countries where baseline iron deficiency was less common(13). The hemoglobin response to iron supplementation appears related to the baseline prevalence and etiology of anemia and the local malaria endemicity(14). Routine iron supplementation reduces the prevalence of anemia among populations in non-malaria endemic areas by 37.9% to 62.3%, but by only 5.8 to 31.8% in malaria hyperendemic regions(15).

DOES IRON AND FOLIC ACID SUPPLEMENTATION INCREASE MALARIA RISK?

Epidemiologic evidence

A summary of previous published studies conducted in young children living in malaria endemic regions is shown in ***Table* I**. Two systematic reviews have been published. Shankar(30) identified an increase in slide positive falciparum malaria among those receiving iron supplementation, but no significant change in clinical malaria episodes. Gera and Sachdev could not identify a significant increase in malaria slide positivity(16). More recent studies have compared intermittent prophylactic treatment (IPT) for malaria with and without iron, to iron alone, and found that groups receiving iron have improved haematological benefits, but with non-significant increases in adverse malarial outcomes(18).

In 2006, results of a double masked, placebo controlled, randomized controlled trial conducted in Tanzania, Africa, an area with high malaria transmission ('the Pemba study'), were published(29). This study compared IFA alone (n=7950), IFA with zinc (n=8120), and placebo (n=8006) to children aged 1 to 35 months and was designed with adequate power to detect the effects of IFA supplementation on mortality. Iron (12.5 mg) and folic acid (50 mg) were administered as dispersible tablets, and all children received Vitamin A. The trial arms administering IFA were discontinued after 20 months, as there was an overall increase in deaths (relative risk 1.61, 95% confidence interval 1.03–2·52), serious adverse events (relative risk 1.32, 95% CI 1.10–1.59), and hospital admissions (relative risk 1.28, 95% CI 1.05–1.55) in the IFA group. Serious events due to malaria (relative risk 1.16, 95% CI 1.02–1.32, P<0.05) and cerebral malaria (relative risk 1.22, 95% CI 1.02–

TABLE I IRON SUPPLEMENTATION STUDIES EVALUATING MALARIA RELATED OUTCOMES IN YOUNG (UNDER 5) CHILDREN LIVING IN MALARIA ENDEMIC AREAS

Author	Year	Country	Sample size	Intervention route, dose	Age group	Malaria related outcomes	Effect
Oppenheimer, *et al.* (19)	1986	Papua New Guinea	Intervention 236 Placebo 250	Single dose iron dextran (150 mg elemental iron) IM*	2 mo	Clinical malaria episodes, lower respiratory tract infections, admissions with evidence of malaria	NS Increased $P<0.05$ Increased $P<0.05$
Smith, *et al.*(20)	1989	Gambia	Overall 213	Oral iron*	6 mo - 5 years	Increased parasitaemia, splenomegaly	Increased $P<0.025$ Increased $P<0.05$
Chippaux, *et al.*(21)	1991	Togo	Intervention 95 Control 95	Oral iron 2.5 mg/kg/ day, 3 months*	6-36 months	Malaria parasitaemia	NS
van Hensbroek(22)	1995	Gambia	Iron 167 Folic Acid 175 Placebo 162	Treatment for malaria (SP or chloroquine) Iron sodium edentate: 27.5mg thrice daily (wt <20kg); 41.25mg thrice daily (wt >20kg)*	6 mo-9 years	Prevalence of malaria (iron group)	NS
Van den Hombergh, *et al.*(23)	1996	Tanzania	Intervention 50 Placebo 50	Oral iron 200mg/d for 3 months + folate *vs*. folate alone†	<30 months;	Extra attendance for care all diagnoses, pneumonia, rate of parasitaemia	Increased $P<0.05$ Increased $P<0.05$ Increased $P<0.05$NS
Menendez, *et al.*(24)	1997	Tanzania	Intervention 204 Placebo 207	Oral iron 2mg/kg, 16 weeks (also antimalarial +/- iron arms)*	2 to 6 months	Clinical episodes of malaria.	NS
Berger, *et al.* (25)	2000	Togo	Intervention 100 Placebo 97	Oral iron 2-3mg/kg/day, 3 months*	6-36 months (Hb >80g/L)	Incidence of infections/ malaria	NS
Verhoef(26)	2002	Kenya	Per group 82	iron (6 mg/kg/wk ferrous fumarate) *vs.* SP *vs*. Iron + SP *vs*. Placebo, 12 weeks*	2-36 months	Clinical malaria attacks SP at baseline (all children)	NS
Desai(27)	2003	Kenya	Iron + SP 129 Iron alone 127 SP alone 127 Placebo 109	Iron (3-6mg/kg ferrous sulphate) +intermittent SP vs Iron alone vs SP alone vs placebo, 12 weeks*	2-36 months	Malaria parasitemia, clinical malaria, clinic visits, non-malaria morbidity	NS NS NS NS
Mebrahtu(28)	2004	Tanzania	Iron 340 Placebo 344	Iron 10 mg/d*	4–71 months	Malaria positivity, parasite density	NS NS
Sazawal(29)	2006	Tanzania	Iron + FA 7950 Iron + FA + zinc 8120 Placebo 8006	Iron 12.5mg Folic acid 50mcg†	1-35 months	Clinical malaria, deaths, hospital admissions, serious malaria episodes, cerebral malaria	Increased $P<0.05$ Increased $P<0.05$ Increased $P<0.05$ Increased $P<0.05$ Increased $P<0.05$

** Supplementation/ treatment with iron alone; † Supplementation/ treatment with iron and folic acid; SP = sulphadoxine + pyrimethamine; FA= Folic acid.*

1·46, *P*=0.03) were increased in the group receiving IFA. Hemoglobin and zinc protoporphyrin were evaluated in a sub-study within the main trial. Baseline anemia (hemoglobin <10g/dL) and iron deficiency (zinc protoporphyrin>80.0 micromol/mol haem) were 57% and 75%, respectively. Post hoc analysis revealed that iron deficient, anemic children given IFA were protected from malaria related events compared with placebo (relative risk 0.56, 95% CI 0.32–0·97); however there was no benefit in iron deficient, non-anemic children, and there was a trend towards harm in non-iron deficient children.

A simultaneous study of similar design and sample size was conducted in Southern Nepal, a non-malaria endemic region. This study (the "Nepal Study") identified no evidence of harm from IFA supplementation in terms of mortality, despite having 29,097 child years follow up. Among groups receiving IFA, iron deficiency anemia was less common (IFA 4% *vs*. placebo 26%, *P*<0.004) and mean hemoglobin higher (IFA 11.11g/dL *vs.* placebo 10.31g/dL, *P*<0.01)(31).

Potential pathogenic mechanisms

Acquisition of iron from the host is essential for survival of pathogenic organisms, and the "nutritional immunity" hypothesis proposes that withholding iron represents a host response to infection and inflammation. Availability of iron for invading organisms is restricted by downregulation of cellular surface transferrin receptors, along with an increase in synthesis of ferritin, shifting iron stores to unavailable compartments(32). *Plasmodia* species may be particularly disadvantaged by iron deficiency since *Plasmodia* appear to rely on the labile pool of intracellular iron, rather than plasma transferrin bound or intracellular heme iron(33,34).

Sulphadoxine and pyrimethamine (SP) is a cheap, frequently used antimalarial combination which acts against parasitic folate synthesis, inhibiting malarial dihydrofolate reductase (DHFR)(35). There are concerns that folic acid supplementation may reverse this inhibition, resulting in treatment failure(36). Malaria patients treated with SP who received iron with folic acid had a higher rate of residual parasitemia after day 7 compared with those who received iron alone, but no difference in clinical failure rates were noted(37). Late treatment failure after treatment for malaria with SP has been associated with elevated blood folate concentrations(38). Interestingly, the authors of the Pemba study did not find an increased risk of malaria recrudescence in the IFA arms, despite routine treatment with SP(29).

Differences in malaria transmission between India and Africa

India is regarded as malaria endemic(39) with 1,50,605 cases of malaria reported in children under 5 years of age in 2002(40). Although most parts of India experience fewer than 2 cases per 1000 population, in 2006 there were almost 17 lakh cases and 1487 deaths due to malaria. Orissa accounts for approximately 25% of the national burden, but substantial transmission also occurs in Jharkhand, West Bengal, the North East States, Chhattisgarh, Rajasthan, Gujarat and Uttar Pradesh(41).

Despite a much smaller population (33.4 million), the number of cases of malaria among children in Tanzania (3.4 million) is far higher than those reported in India (0.15 million) in 2002(41). Transmission in Tanzania is holoendemic, whereas Indian transmission patterns are heterogeneous, with well-circumscribed malaria-endemic areas, areas of seasonal transmission, malaria-free regions, and areas with episodic outbreaks. Although the contribution of malaria to the overall burden of anemia in India is not as well documented as in Africa(42), the state wise distribution of childhood anemia prevalence and cases of malaria suggests both conditions must often coexist (***Table* II**). The number of infective bites per person per night is lower in India than in Pemba Island(43,44). Data regarding malaria transmission is available in only a few parts of India, particularly Orissa and the North East states.

DOES IRON SUPPLEMENTATION INCREASE RISK OF NON-MALARIAL INFECTIONS?

In India, acute respiratory infection and diarrhea remain the leading causes of non-neonatal mortality among children. About 20% of all under-5 deaths in India between 2000 and 2003 were due to diarrhea,

TABLE II ANEMIA AND MALARIA BY STATE, INDIA, 2005

State	Total Population (million)*	% children aged 6-59 months with anemia (Hb<11g/dL)†	Number of slides positive for malaria‡	Slides positive per million population§	No. of cases (%) Falciparum malaria	Deaths recorded from malaria
North						
Delhi	13.7	57.0	1133	82.7	61 (5.4)	0
Haryana	21.1	72.3	33262	1576.4	238 (0.7)	0
Himachal Pradesh	6.1	54.7	129	21.1	0 (0)	0
Jammu and Kashmir	10.1	58.6	268	26.5	7 (2.6)	0
Punjab	24.3	66.4	1883	77.5	28 (1.5)	0
Rajasthan	56.5	69.7	52286	925.4	4061 (7.8)	22
Uttaranchal	8.5	61.4	1242	146.1	17 (1.4)	0
Central						
Chattisgarth	20.8	71.2	187950	9036.1	140182 (74.6)	3
Madhya Pradesh	60.4	74.1	104317	1727.1	32250 (30.9)	44
Uttar Pradesh	166.1	73.9	105303	634.0	3149 (3.0)	0
Eastern						
Bihar	82.9	78.0	2733	33.0	427 (15.6)	1
Jharkand	26.9	70.3	193144	7180.1	51676 (26.8)	21
Orissa	36.7	65.0	396573	10805.8	342692 (86.4)	255
West Bengal	80.2	61.0	185964	2318.8	41365 (22.2)	175
North East						
Arunachal Pradesh	1.1	56.9	31215	28377.3	7447 (23.9)	0
Assam	26.6	69.6	67885	2552.1	45453 (67.0)	113
Manipur	2.4	41.1	1844	768.3	641 (34.8)	3
Meghalaya	2.3	64.4	16816	7311.3	14758 (87.8)	41
Mizoram	0.9	44.2	10741	11934.4	6294 (58.6)	74
Sikkim	0.5	59.2	69	138.0	31 (44.9)	0
Tripura	3.2	62.9	18008	5627.5	14261 (79.2)	20
Western						
Goa	1.3	38.2	3747	2882.3	468 (12.5)	1
Maharashtra	96.8	63.4	47608	491.8	16718 (35.1)	104
Gujarat	50.6	69.7	33262	657.4	238 (0.7)	0
Southern						
Tamil Nadu	62.1	64.2	39678	638.9	3098 (7.8)	0
Andhra Pradesh	75.7	70.8	39099	516.5	22548 (57.7)	0
Karnataka	52.7	70.4	83181	1578.4	21984 (26.4)	26
Kerala		44.5	2554	80.3	337 (13.2)	6

** Based on Census of India, 2001(43); †Based on National Family Health Survey 3(1); ‡Based on National Malaria Control Program data per state 2005(44); §Calculated by dividing number of slide positive cases by total population in millions.*

and 19% due to pneumonia(45). This is not dissimilar to the etiology of deaths in the Nepal study, where out of 353 deaths across all three arms, 106 (30.0%) were due to diarrhea or dysentery, and 77 (21.8%) due to acute respiratory illness(31). Tuberculosis and HIV infection account for approximately 1% of deaths in children under age 5 in India.

A 2001 review of iron supplementation trials in malaria-endemic regions showed a significant increase in respiratory tract infection rates in 2 of 5 studies; an increase in other non-malarial infectious disease in 4 of 8 studies, but no associations with IFA and diarrhoea; pooled analysis was not performed(17). A subsequent meta-analysis of randomized controlled trials exploring iron supplementation effects on infectious diseases found that the incidence rate ratio of diarrhea was significantly higher in iron supplementation groups (11% higher risk of developing diarrhea, $P<0.05$, 17 studies), with a rate difference among those receiving oral iron (9 studies) of 0.18 episodes per child year (–0.01 to 0.37; $P=0.07$). The authors found that iron supplementation did not increase respiratory infection(16). The Nepal study found no significant difference in acute or chronic diarrhea, dysentery, acute respiratory illness, or deaths from diarrhoea or respiratory illness, between groups receiving IFA and placebo(31). In contrast, participants in the IFA arms of the Pemba study did experience an overall increase in mortality from infections other than malaria (pneumonia, meningitis, sepsis, pertussis and measles)(29).

Concerns have been raised about the risks of IFA supplementation among children with human immunodeficiency virus (HIV) or tuberculosis infection. It has been proposed that iron may activate nuclear transcription factors such as NF-kappa B that could potentially enhance HIV replication(46). Cohort studies in adults in non-malaria endemic areas have suggested an association between mortality and faster HIV disease progression in groups with higher iron stores(47,48). The etiology of anemia in tuberculosis appears to be mediated by inflammation, rather than iron deficiency(49). A recent Cochrane review concluded that there is a dearth of evidence evaluating the effect of IFA among children with HIV or tuberculosis, particularly in areas of high prevalence of HIV, malaria and iron deficiency anemia, and that urgent prospective randomized trials are needed to guide public policy(50).

DISCUSSION

In response to the findings of the Pemba study, the WHO has amended its guidelines, recommending that where malaria transmission is intense and infectious diseases highly prevalent, "iron and folic acid supplementation be targeted to those who are anemic and at risk of iron deficiency," with meticulous attention to prevention and treatment of malaria and other infectious diseases(51). No change to the IFA supplementation policy has been proposed for malaria non-endemic regions.

Should a single randomized study alter global, and in particular, Indian policy given that previous meta-analyses have not conclusively identified an increase in malaria related adverse outcomes or mortality in children receiving iron supplementation? The total number of participants examined in the studies included in the review by Gera, *et al*.(15) was 1207 for iron supplementation and 1183 for control, far smaller than the sample sizes of Pemba and Nepal studies. Pre-2006 meta-analyses may therefore be underpowered to detect an increase in malaria related mortality due to IFA supplementation (type II error)(52). The size of the Pemba study provided adequate power to detect adverse mortality effects and thus its results are sufficient to influence policy.

Regarding the benefits of IFA supplementation, meta-analyses reviewing the effects of iron supplementation on cognitive, motor and physical development have been inconclusive(12,13,53). Nevertheless, providing IFA to iron deficient, anemic children did improve survival among the Pemba sub-study cohort, whilst meta-analyses suggest improvement in mental development scores in children receiving iron where the prevalence of baseline iron deficiency is high(12), suggesting correcting iron deficiency is beneficial. The influence of routine IFA supplementation on diarrhea and acute respiratory infection appears negligible in

KEY MESSAGES

- Routine iron and folic acid is recommended for all children under 6-60 months years by the National Nutritional Anemia Control Program
- In regions of India where malaria transmission is uncommon and access to primary health care is good, routine IFA supplementation should continue for all young children, regardless of anemia status.
- In areas of high malaria transmission in India, routine supplementation of IFA to young children may be withheld, with emphasis on clinical case detection and treatment of anemic children.
- There is a need for randomized controlled trials to explore the benefits and risks of iron and folic acid supplements in different areas of India.

non-malaria endemic areas, but may be more important in malaria endemic regions.

Differences in vector biology, malaria transmission rates and host-parasite responses between Africa, Nepal and India should be considered when extrapolating trial results between regions. Furthermore, caution is required when applying the results of studies conducted in one geographic area to a different region. The Nepal study highlighted that although there was no survival benefit from IFA supplementation, there is no evidence of harm. This suggests that IFA supplementation to young children in non-malaria endemic regions of India is safe.

RECOMMENDATIONS

Based on the evidence reviewed, we propose the following approach.

1. Where malaria transmission is uncommon and access to primary health care is good, routine IFA supplementation should continue for all young children, regardless of anemia status, as recommended by the NNACP. In such regions, IFA is likely to be safe given the results of the Nepal study.
2. Based on the Pemba Study's finding of harm from routine IFA supplementation in malaria-endemic areas, we recommend that in areas of highest malaria transmission in India, and where access to primary health care is suboptimal, routine supplementation of IFA to young children may be withheld; instead, clinical case detection and treatment of anemic children should be adopted in these settings. Routine supplementation should be considered only once malaria control and primary health infrastructure have been strengthened.

Several issues will need to be addressed to enable practical implementation of these recommendations. For instance, malaria endemicity thresholds and malaria transmission levels (for example, entomological inoculation rates) should be defined comprehensively at the local level in the Indian setting. Furthermore, quality of access to primary health care will need to be defined regionally to enable assessment of the likely capacity for services to treat cases of infectious diseases. These steps will be necessary in order to rationalize iron supplementation programs so that they are targeted towards those who would most benefit and withheld from those at risk of harm. Finally, there is a need to conduct well-designed trials explore the mortality and morbidity benefits of IFA supplementation in the Indian context. This would be of great value in guiding health care policy related to iron supplementation in the Indian subcontinent.

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