

Reducing anaemia in low income countries: control of infection is essential

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Standfirst

Iron interventions are the mainstay of recommendations to combat the enormous global burden of anaemia; however recent scientific and epidemiologic insights suggest that in settings with high infection burden, this strategy is neither

satisfactorily safe nor effective and that to improve outcomes, control of infection must receive equal emphasis.

Introduction

Anaemia affects 273 million children and 529 million women globally,¹ accounting for 8.8% of all years lived with disability.² Anaemia prevalence in children under-5 years is highest in sub-Saharan Africa (62.3%) and South-East Asia (53.8%),¹ where rates of concomitant infection are also high. Between 1993-2011, the estimated anaemia prevalence worldwide only fell from 33% to 29% in non-pregnant women and from 47% to 43% in pre-school children.³ The 2016 Global Nutrition Report found that progress towards the WHO target of 50% anaemia reduction in women by 2025 is 100 years behind schedule.⁴

Iron is an essential micronutrient required for many biological processes including oxygen transport, mitochondrial function, and numerous enzymatic pathways. Iron deficiency can therefore compromise diverse physiological functions and ultimately leads to anaemia. Public health strategies to control anaemia emphasise iron replenishment: food fortification with iron, universal distribution of iron supplements, and home-fortification of complementary foods with iron-containing multiple micronutrient powders (MNPs).⁵⁻⁷ Failures in resolving the anaemia burden have been attributed to programmatic limitations: problems with financing, supply, distribution or adherence to interventions.^{4,8} However, as discussed in this article, new understanding of iron-infection interactions, evidence from clinical trials, and anaemia epidemiology cast doubt into the safety and prominence of universal iron interventions as the mainstay of public health anaemia control, especially among young children in areas of high infectious burden. Although this has stimulated modifications to WHO iron intervention guidelines, a further change of approach to anaemia control is needed.

New insights into iron-infection interactions

Anaemia control policy in children was upended in 2006 by a large trial in Pemba, Tanzania, that was prematurely terminated due to an increase in risk of death and hospitalisation, besides other serious infection related events, among children randomized to iron/folic-acid (Box 1). Although a parallel trial in (non-malaria-endemic) Nepal did not detect these adverse effects, the Pemba study provoked urgent policy changes,⁹ reinvigorated clinical, epidemiologic and experimental research addressing iron-infection interactions, and coincided with rapid advances in fundamental understanding of iron biology. This work, which we describe below, highlights the importance of infection control in public health prevention and control of anaemia.

1. Humans have evolved to withhold iron from the plasma during infection

The discovery that hepcidin, the master iron-control hormone, is an inflammation-regulated acute-phase peptide highlights the direct interaction between iron homeostasis and innate immunity.¹⁰ Hepcidin is secreted mainly by hepatocytes, causing internalization and degradation of the sole iron exporter ferroportin on macrophages and duodenal enterocytes, thereby preventing iron egress.¹¹ Hepcidin upregulation during infection inhibits dietary iron absorption and macrophage release of recycled iron resulting in acute reductions in plasma iron levels; this impairs bacterial growth in plasma¹² but simultaneously starves developing red cells of iron.

At the high doses typical in supplements, oral iron can overwhelm natural hepcidin-mediated constraints on iron absorption.¹³ Treating patients with iron supplements elevates transferrin saturation, providing a medium which enhances microbial growth (e.g. *E coli*, *Yersinia*, *Salmonella*) in *ex vivo* assays.¹⁴ Furthermore, iron deficient individuals more efficiently absorb iron supplements, resulting in a spike in plasma

iron that can temporarily overcome transferrin's binding capacity, causing appearance of non-transferrin bound iron (NTBI)¹⁵ which enhances growth of virulent pathogens such as *Yersinia* and *Vibrio* species.¹⁶ Thus, at high doses, iron supplementation may promote pathogen growth by overcoming the hepcidin-mediated iron-starvation response to inflammation.

2. Iron deficiency protects children against malaria, and iron administration poses a transitory risk for malaria

Cohort studies in Malawi and Tanzania showed that preschool children with baseline iron deficiency living where malaria transmission is intense and where no prophylaxis was distributed have a substantially reduced risk of subsequent malaria parasitaemia, clinical malaria, severe malaria, and all-cause and malaria-specific mortality.^{17 18}

Correspondingly, two iron intervention studies indicate that treating iron deficiency with iron increases malaria susceptibility. After receiving MNPs containing 18mg iron (with or without zinc), iron deficient Tanzanian children experienced a 41% increased malaria risk after receiving MNPs, while no increased risk was found among iron-replete children.¹⁹ Likewise, increased malaria incidence was found in Malawian HIV-infected anaemic children in the first three months following iron supplementation.²⁰

Although a 2016 Cochrane review found no overall effect of iron interventions on clinical malaria risk in children, subgroup analysis stratifying by malaria prevention/treatment access revealed that clinical malaria risk increased by 16% [2%-31%] when iron was administered without co-provision of prevention/treatment, but declined by 9% [16%-3%] when administered with control measures.

Furthermore, iron increased *Plasmodium* parasitaemia risk by 11% [0%-23%] during supplementation, and by 23% [9-40%] in the post-supplementation period,²¹

supporting the cohort study findings described above. The consequent 2016 WHO guidelines therefore require that iron interventions only be given where strategies to prevent, diagnose and treat malaria are operational; however, malaria control in settings where iron interventions may be recommended is frequently suboptimal (see section 7).

The above data are supported by experiments demonstrating preferential *P. falciparum in vitro* infection of erythrocytes from iron replete and recently iron-supplemented donors, over those from iron deficient donors (with donors comprising healthy US adults²² and Gambian children receiving iron-containing MNPs.)²³ Merozoites preferentially invade young erythrocytes (reticulocytes), which increase during anaemia recovery following iron treatment, providing a mechanistic explanation for these observations.²² Another recent study observed protection from clinical malaria and parasitaemia in Ghanaian pregnant women and Zambian children carrying the ferroportin Q248H mutation, shown previously to reduce ferroportin's hepcidin sensitivity.²⁴ Correspondingly, mice with erythoblast-specific ferroportin knockout were rendered susceptible to murine malaria, associated with increased red cell iron.

Together, these data suggest a cruel paradox - whilst children with iron-deficiency anaemia are most likely to benefit from iron interventions, effective erythropoietic responses following iron places these same individuals at greatest risk through enhancing malaria susceptibility. Any solution that delivers iron for erythropoiesis and successfully restitutes anaemia by definition induces reticulocytosis, casting doubt that, in malarial settings, any effective iron intervention (supplement, fortificant, food) can be safe unless accompanied by reliable malaria prevention.

3. Malaria is not the only infection exacerbated by iron interventions

In the colon, beneficial bacteria help prevent colonisation by pathogenic species and may not require iron (e.g. *Lactobacilli*). In contrast, iron favours growth of enteric pathogens.²⁵ Unabsorbed iron from supplements, MNPs and fortificants can exacerbate risk of intestinal colonisation by pathogenic species.²⁶ Studies in non-malaria-endemic settings in Pakistan found increased diarrhoea (including bloody-diarrhoea) from iron-containing MNPs,²⁷ besides increased rapid chest indrawing, raising concern iron may also exacerbate respiratory infection risk. Contrastingly, the large Nepal trial (Box 1) found no effects from supplemental iron on infections including diarrhoea.²⁸ Nevertheless, systematic reviews published in 2016, 2013 and 2002 (i.e. before these large trials) each found that iron interventions increased diarrhea risk (by 15% [6-26%]²¹, 4% [1-6%]²⁹ and 11% [1-23%]³⁰ respectively).

Studies evaluating how iron fortification influences intestinal microbiota provide a plausible mechanism underlying increased diarrhea following iron administration. Ivorian children given iron-fortified biscuits displayed reduced commensal lactobacilli, increased pathogenic enterobacteria and elevated intestinal inflammatory biomarkers.³¹ Likewise, increased carriage of intestinal pathogens including *Escherichia*, *Shigella* and *Clostridium* and intestinal inflammation was found in Kenyan infants receiving iron-containing MNPs.²⁶ Such effects were not observed in South African children with low baseline prevalence of pathogenic bacteria, suggesting a harmful effect of iron on intestinal microbiota may manifest in settings where carriage of pathogenic species is already prevalent, perhaps relating to underlying water, sanitation and hygiene (WASH) conditions. These trials were not powered to discern effects on gastrointestinal illness.

4. Control of malaria alone may decrease iron deficiency

Symptomatic and asymptomatic malaria parasitaemia inhibits iron absorption via hepcidin upregulation. In Beninese women with asymptomatic *P. falciparum* infection, anti-malarial treatment increased mean dietary iron absorption from 10% to

18%.³² Complementing this, the prevalence of iron deficiency and iron deficiency anaemia was significantly higher at the end than at the start of malaria seasons in rural West and East African pre-school children, suggesting suppression of iron absorption by infection.³³ Moreover, interruption of malaria transmission for 12 months in rural Kenya reduced the prevalence in young children of iron deficiency from 35% to 26%, and anaemia from 54% to 32%.³⁴

Cochrane reviews indicate that malaria control can improve haemoglobin or reduce anaemia: for example intermittent preventive therapy (IPT) reduces moderate anaemia by about 40% in pregnant women³⁵ and 29% in children;³⁶ bednet use increased haematocrit by 1.5%;³⁷ and indoor residual spraying improved haemoglobin by 0.85g/dL (based on a single trial).³⁸ Thus, malaria control alone may alleviate iron deficiency and anaemia even without iron provision.

5. Iron supplementation to pregnant women in malaria endemic areas is likely safe and improves child outcomes

Two large trials have recently evaluated effects of antenatal iron supplementation on malaria risk during pregnancy. In Kenyan women, there was no evidence of increased clinical malaria, placental malaria or parasitaemia among women randomized to oral iron, even among women who received limited or no IPT.³⁹

Importantly, iron yielded clear benefits to both mother and child increasing birth weight by 150g, lengthening gestation duration by 3.4 days and reducing risk of low birth weight and premature birth by 58% and 7% respectively. Benefits were enhanced among women with baseline iron deficiency. Similar benefits of iron have been identified previously,^{40 41} but this trial was one of the first to include women with anaemia, potentially explaining the large impact on birth outcomes. In a second recent placebo-controlled trial in non-iron deficient, non-anaemic, pregnant Tanzanian women, iron supplementation did not increase placental malaria, although

no benefit on birth weight or gestation duration was observed, perhaps reflecting higher baseline iron status in this study population.⁴² These trials indicate that antenatal iron supplementation is safe even where malaria is highly endemic and malaria control strategies incompletely implemented (perhaps due to more developed host-immunity and/or tolerance to pathogen load in adulthood),⁴³ and have important benefits on maternal and neonatal health when iron deficiency is prevalent. Detailed investigations of potential risks from iron in pregnancy on other infections are still warranted.

6. The proportion of anaemia that is iron-responsive is lower than previously estimated

Previously, at least half of anaemia cases were attributed to iron deficiency and so potentially iron-responsive. Anaemia prevalence in preschool children is highest in Africa, the Eastern Mediterranean, and Asia, in these settings, WHO estimates that in preschool children only 32%, 38% and 41% of anaemia respectively (42% globally) is iron-responsive.¹ These figures are higher among women.¹ Thus, non-iron-responsive anaemia is prevalent in young children in low-income, high-infection settings - both malaria-endemic and non-endemic. The population response to iron is likely determined by the proportion of individuals able to absorb and utilise iron for erythropoiesis. Physiologically, iron absorption/utilization is determined by hepcidin status: in a study of 1313 Gambian and Kenyan infants, we found that only 27% had hepcidin concentrations below the threshold permitting effective iron absorption and utilisation.⁴⁴

Causes of anaemia beyond iron deficiency in these settings may include anaemia of inflammation, malaria, and carrier-states for or clinically evident inherited red cell disorders (e.g. thalassaemia, sickle cell disease and G6PD deficiency).

Co-existent multiple micronutrient deficiencies (e.g. of other haematinic micronutrients or vitamin A) could impair the haemoglobin response to iron. Vitamin A deficiency may impair immune function, exacerbating infection risk, promoting inflammation and impairing iron utilisation. Studies testing effects of vitamin A supplementation (with or without iron) on anaemia have yielded mixed results.⁴⁵ Data comparing MNPs to iron supplements alone in children are lacking although in pregnancy, a meta-analysis of four trials found no additional benefit from MNPs on anaemia compared with iron alone.⁴⁶

Environmental enteropathy (EE) is a subclinical malabsorptive condition highly prevalent among children in low income countries, attributed to recurrent infection and chronic malnutrition, and characterised by intestinal villous atrophy, impaired barrier function, and intestinal inflammation.⁴⁷ The role of intestinal functional impairment on iron absorption remains unclear, and causal links between EE and iron deficiency or anaemia have not yet been defined; however, it remains plausible that failure of luminal absorptive function may render anaemia non-iron responsive.

Diagnosis of anaemia aetiology remains challenging in resource poor settings: biomarkers for iron deficiency remain expensive and difficult to interpret with concurrent inflammation, while sophisticated red cell testing is difficult to implement routinely in the field. The epidemiology of these conditions should be considered when planning anaemia control programs, as treatment of non-iron deficiency anaemia with iron is at best ineffective, and in settings with high infection burden, may increase risk of harm.

7. Implementation of malaria prevention is frequently inadequate for safe delivery of universal iron interventions

WHO guidelines currently recommend universal iron or MNPs where anaemia prevalence exceeds 20-40%, even in malaria-endemic areas, as long as interventions to 'prevent, diagnose and treat' malaria are also provided. The appropriate forms of malaria-control to accompany iron interventions are not defined. For example, insecticide treated bednets reduce the incidence of uncomplicated clinical malaria, but only by about 50%.³⁷ A trial in Ghana where all participants used insecticide-treated bednets did not find increased malaria from iron-containing MNPs, but did find a 23% [2-49%] increase in hospitalization during (but not following) the intervention period, suggesting bednets do not prevent iron-induced increases in serious adverse events.⁴⁸

The coverage of malaria prevention, diagnosis and treatment measures remain inadequate in high-risk settings. The 2016 World Malaria Report indicated that only 57% of at-risk sub-Saharan African populations slept under a bednet (prevention), 56% of febrile children are taken to trained health care providers (diagnosis), and 30% of children with evidence of *P falciparum* infection and a history of fever receive antimalarial drugs (treatment).⁴⁹ Thus, under routine conditions, it is likely that fewer than half of children in malaria-endemic settings would be covered such that iron interventions could be deployed safely; unselected, 'universal' distribution is likely unsafe. Although malaria burden has progressively declined over the last two decades, the 2017 World Malaria Report suggests that gains have plateaued or are even being reversed.⁵⁰

The risk-benefit of iron interventions in infection-endemic regions must be considered

An important consideration prior to iron distribution is whether reductions in anaemia prevalence *per se*, or benefits on functional health outcomes such as development

and growth in young children (that are not yet supported by high quality evidence from randomized controlled trials^{51 52}) justify the increased risk of infections.

Global burden of disease data indicate that in 2016, the Disability Adjusted Life Years attributable to diarrhoea, malaria and iron deficiency anaemia in 1-4 year-old children were 11.1 million, 27.3 million and 1.8 million respectively in sub-Saharan Africa, and 3.5 million, 1.0 million, and 2.4 million respectively in South Asia.⁵³ If iron interventions exacerbate risk of infectious diseases (even whilst reducing anaemia) they may raise the overall burden of disease in these settings. In contrast, controlling malaria and diarrhoea decreases burden of these infections, and by suppressing inflammation and hepcidin, could simultaneously improve iron absorption and utilization and contribute to reducing anaemia burden.

We make policy recommendations in Box 2, and propose critical research priorities in Box 3.

Key messages

- Universal iron interventions designed to alleviate anaemia in young children living in low income countries may exacerbate risk of infection, especially malaria and diarrhoea.
- Iron interventions alone will not resolve the majority of the burden of anaemia in young children living in sub-Saharan Africa and Asia. To achieve anaemia control in high infection burden settings, addressing infection is at least as important as iron interventions. Strategies to control and prevent malaria (and other infections) may improve anaemia burden independently of iron interventions, and if combined with iron, may make iron interventions safer and more effective.
- Iron intervention should be prioritised in pregnant women, where safety has been demonstrated and benefits on maternal and neonatal outcomes are clear.

Box 1: Iron-Malaria policy since Pemba

The Pemba Trial (Tanzania) was powered to demonstrate a survival benefit in children receiving iron, randomising over 24000 children aged 6-36 months to placebo, iron folic acid (IFA), and IFA with zinc. The trial was stopped early because of an increase in death or hospital admission among children randomized to IFA (with or without zinc) (relative risk 1.12 [95% CI 1.02–1.23]). IFA also increased hospital admissions (RR 1.11 [1.01–1.23]), cerebral malaria (RR 1.22 [1.02–1.46]), and serious adverse events (RR 1.32 [1.10–1.59]), deaths (RR 1.61 [1.03–2.52]) and admissions to hospital (RR 1.28 [1.05-1.55]) due to non-malarial infections. A substudy of 2413 children found that infection from iron was only increased in children without elevated baseline zinc protoporphyrin.

A similar trial evaluating IFA in children in a non-malaria endemic setting (Nepal) was published simultaneously. This trial was also designed to demonstrate benefit from iron on child survival, but was terminated prematurely once there was no possibility a beneficial effect would be detected. It found no effects from iron on infections including diarrhoea.²⁸

Following Pemba, WHO suspended its policy of universal iron for children in malaria endemic areas, instead recommending IFA only in anaemic children.⁹ In 2011, based on a Cochrane review, WHO published new recommendations for MNP implementation to children where the prevalence of anaemia is high, stating that in malaria endemic areas, MNPs should be provided only to children with access to malaria preventive and treatment services.⁵ Over the past decade there has been rapid scaling up of MNP programmes. In 2015, up to 50 million children received MNPs.

Updated 2016 WHO guidelines reintroduced daily iron supplementation as a second option (alongside MNPs) in children, and based on an updated Cochrane review,²¹ reiterated that in malaria–endemic areas, iron provision to children “should be done in conjunction with public health measures to prevent, diagnose and treat malaria.” Guidelines further state that “provision of iron ... should not be made to children who do not have access to malaria-prevention strategies (e.g. provision of insecticide-treated bednets and vector-control programmes), prompt diagnosis of malaria illness, and treatment with effective antimalarial drug therapy.”⁷

Box 2: Policy Recommendations

- Reducing the burden of anaemia should be considered an important additional rationale for, and outcome of, programmes to control infectious diseases.
- As recommended by WHO, iron interventions should be withheld from children in malaria-endemic settings unless malaria prevention is provided. We propose that this implies delivery of iron and effective malaria control interventions should have identical coverage – malaria prevention and iron interventions should *converge at the level of the individual child*. In settings of high infection intensity, more aggressive approaches (e.g. beyond bednets alone), such as combining iron interventions with use of malaria chemoprevention, should be explored.
- When effective in raising haemoglobin, the risk of iron exacerbating malaria is likely highest in initially anaemic children. Therefore, when treating anaemic children with iron, they must receive specific attention to malaria prevention during recovery.
- Iron supplementation appears unambiguously beneficial in pregnancy, and hence delivery of and adherence to iron should be prioritised in pregnant women in low income countries.

Box 3: Research needs

- The optimal type of malaria prevention measures to be co-implemented with iron, that render iron interventions safe, should be defined in adequately powered prospective studies. The burden of malaria (e.g. clinical incidence, parasite prevalence, entomological inoculation rate) and coverage of effective malaria prevention strategies at which universal iron interventions can be considered safe should be defined.
- Strategies (technologies and clinical protocols) to improve diagnosis and management of non-iron responsive anaemia in low resource settings should be developed.
- The impact of non-malarial infections (e.g. diarrhoea, respiratory and skin infections, all common in low income countries) on iron absorption should be established. The effect of water, sanitation and hygiene (WASH) interventions on iron absorption and utilisation, iron deficiency and anaemia should be defined.
- The lowest doses of iron in pregnancy that achieve desirable clinical outcomes for mother and baby should be established.
- Functional health benefits from iron provision in young children (e.g. on cognitive and physical development, wellbeing) require precise definition in high quality trials so that evidence-based decisions can be made and risk-benefit analysis can be undertaken.

Author Contributions

Dr Pasricha conceived the manuscript through extensive consultation with other experts in the field at many technical meetings and academic conferences; he wrote the first draft. Dr Pasricha has extensive experience in public health, clinical and scientific aspects of anaemia control and biology, has advised several international organisations on aspects of anaemia control, and leads several large randomised

controlled trials testing efficacy and effectiveness of anaemia control interventions. Dr Armitage and Prof Drakesmith are experts in iron-infection interactions through experimental biology. Prof Prentice leads several trials aimed at addressing anaemia burden in children, and advises several international governmental and non-governmental agencies on nutrition policy. All authors wrote, edited and approved the final manuscript. SP is guarantor for this manuscript.

Conflicts of interest

We have read and understood the BMJ Group policy on declaration of interests and declare the following interests: Dr. Pasricha reports grants from Medical Research Council UK, grants from Bill & Melinda Gates Foundation, grants from the National Health and Medical Research Council Australia, and grants from Cooley's Anemia Foundation during the conduct of the study. Drs Armitage, Prentice and Drakesmith report grants from Medical Research Council UK, grants from Bill & Melinda Gates Foundation. Dr. Drakesmith reports support from BRC Blood Theme, NIHR Oxford Biomedical Research Centre, Oxford, United Kingdom.

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