Did the “iron age” end in Pemba?

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The dilemma of iron supplementation in malaria-endemic regions

Until 2006, micronutrient supplements in the order of recommended dietary allowance (RDA) dosages, including that for iron, were considered inherently safe (1). The RDA values for iron for children in this age bracket are based on estimates to cover the requirements for growth and metabolism and to replace iron losses. The corresponding upper level (UL) for safe dietary intake in children is 40 mg Fe/d (2), based on side effects after oral intake in the form of supplements; this suggests a relatively broad margin of safety for iron in children. In this context, the WHO recommendation to supplement 12.5 mg Fe + 50 µg folic acid when the prevalence of anemia exceeded 40% in children 6–36 months of age (3) seemed safe and prudent. This continuum of assumptions was severely disturbed when an excess number of hospital admissions and deaths occurred in malaria-exposed children during iron supplementation (4).

Iron is essential for the malaria pathogen, *Plasmodium falciparum*, and for its human hosts alike. During their intra-erythrocyte stages plasmodia cannot access the erythrocytes’ ample heme iron content; for rapid reduplication they depend on adequate non-heme iron supply. As most malaria-endemic areas are located within the tropical iron-deficiency belt, iron supplementation programs performed in these regions are likely to relieve iron-deficiency in the human population, but also in plasmodium parasites. As reviewed by Oppenheimer (5), two questions emerged regarding iron status and malaria outcomes: Data from a considerable number of studies were conflicting as to whether supplemental iron is more beneficial for the pathogen or the host, or whether low iron status is

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Hemoglobin structure

Malaria transmission risk areas.  
From WHO-UNICEF World Malaria Report 2005
protective against the ravages of malaria.

These questions prompted a large trial on the impact of low-dose, daily iron-folate supplementation in infants and toddlers 6–36 months of age on the island of Pemba; this is a region with high malaria transmission rates in the Zanzibari island chain off the coast of Tanzania in East Africa. The carefully designed and well-conducted study compared the impact of routinely supplementing 12.5 mg Fe + 50 μg folic acid/d with or without 10 mg of Zn as compared to placebo in approx. 8000 subjects in each study arm. The frequency of hospital admission and the prevalence of deaths in the course of malaria-attacks were chosen as end-points. The statistical power of this study exceeded the sum of all earlier trials on the subject of the interaction of iron supplementation with endemic malaria. Iron status was assessed by determination of serum ferritin and erythrocyte protoporphyrin (with AGP-I/α1-glycoprotein as inflammatory marker) in a subgroup of approx. 1500 infants in each study arm. Moreover, plasmodia parasite density and the prevalence of accompanying pneumonia and encephalitis events were registered during malaria attacks. Due to increased death rates and significantly higher hospital admission rates in the two iron/folic acid-supplemented groups, the study was discontinued after 18 months in the two groups supplemented with iron and folic acid (4).

This finding on Pemba Island has put iron-supplementation programs in malaria-endemic areas on the horns of a dilemma: On the one hand, it has long been discussed that iron deficiency predisposes infants to excessive infectious morbidity (6). Moreover, iron-deficiency anemia during the first 18 month of life is assumed to impair cognitive development irreversibly (7). All of this strongly argues for intervention programs to combat iron deficiency anemia (IDA) in early life. On the other hand, a public intervention program that risks an increase in hospital admissions and death of children seems to be as ethically unacceptable as it would be to leave iron-deficient children to their fate.

A parallel trial with a similar design, intervention protocol, and magnitude as the Pemba study was performed in Nepal (8). In this non-malarial setting, no increased nor decreased risk for hospital admission or death was associated with iron supplementation in infants. Therefore, the call to revise recommendations in preschool iron supplementation programs, on the basis of these recent revelations (4, 8), is primarily restricted to malaria-endemic areas. Although the Nepal trial found no reduced rates of morbidity or death after iron supplementation as compared to controls, the cited effects of infant iron deficiency on morbidity and impaired intellectual development mentioned above still militate strongly in favor ofIDA mitigation programs.

Iron-deficient and anemic infants and toddlers coexist by side with iron-sufficient peers in all locations, even where more than 40% of the population is anemic.
Moreover, some of the endemic anemia in early life will be attributable to causes other than iron deficiency. The Pemba findings (4) put into relief the potentially problematic nature of one-size-fits-all solutions in public health. Many valuable and positive lessons can be derived from the Pemba saga and its aftermath. First, the Data Safety Management Board of the study was vigilant, and implemented measures to mitigate subjects’ risk in a timely and transparent manner. The overseeing entities appropriately terminated the iron supplementation arms of the study.

Considerations on the folic acid component

It is worth bearing in mind that iron was not the only common factor in the “iron treatment” groups; each daily supplement contained also 50 μg of folic acid. It has been suggested that simultaneous administration of folic acid may be deleterious, since anti-folate metabolites are the basis of anti-malarial medications used to treat malaria attacks (9). Though this comment deals with the safety of iron administration, it should be understood that a comprehensive approach to malaria prevention requires other measures in parallel, such as insecticide-treated bed nets and malaria medication.

How can the dilemma be tackled?

As observed in several commentaries (10, 11), iron is a particular “problem nutrient” for complementary foods fed in the weaning period. Some guidance is available, though, to cut this “Gordian knot” of the supplement or no-supplement dilemma for young children. Firstly, alternative approaches to ease iron-deficiency, other than routine, daily iron supplementation, should be considered. These include measures such as delayed cord clamping during birth, increasing food choice and food security, providing iron-fortified complementary foods and implementing hookworm treatment programs in endemic areas. Specifically within the domain of food choice is the recent notion to rely more heavily on the heme iron of muscle and organ meat (11). It is suggested, from contemporary hunter-gathers, that the evolutionary weaning food was pre-masticated meat. This is rich in highly bioavailable heme-iron.

When the usual cereal gruels or paps are part of the weaning culture, liberation of the iron from the iron-phytate complexes comes in as a potentially feasible strategy to provide greater uptake of iron from traditional grain-based complementary foods (12). The most basic approaches to phytate reduction involve soaking or germination of the seeds (13). Specific low-phytate varieties of grains, such as maize, have been developed. A substantial increase in iron absorption efficiency was seen from corn tortillas prepared from low-phytate maize (14). Fungal phytase preparations, capable of digesting phytate in the dough or even within the digestive tract have been developed (15). However, when considering children as young as 6 months of age, any exposure toundenatured fungal allergens should be limited.

A final approach to improving iron delivery and to prevent or reverse IDA in infants in malarial areas would be the application of oral iron supplements, but with specific precautions to mitigate the adverse consequences seen in the Pemba experience (4). These mitigating strategies are detailed in the following section.

Can the safety of supplemental iron administration in malaria-regions be improved?

In addition to the alternative approaches mentioned above it may be necessary to entertain the notion of administering supplemental forms of iron to young children in malarial areas. Are there approaches that can improve the safety? Two caveats to the current practices can be identified. The first comes from an analysis of a subgroup with hematological evaluation in the Pemba trial. It showed that when a child in the iron-intervention arms of the study was actually iron deficient, he or she benefited from iron supplementation; it improved iron and hemoglobin status, while decreasing the number of hospital admissions, concomitant infections, and fatalities related to malaria. Iron-replete children, in contrast, had an increased risk for such events. Thus, the dilemma might be resolved, if the iron status in all participants of a public health supplementation program and their response to iron intervention could be monitored. All currently available options, however, have three drawbacks: 1) They add considerable costs to IDA mitigation programs; 2) They have yet to be tested for their applicability in the field; and 3) They generally involve the sampling of
blood, with all that implies for discomfort to the child, acceptability to the families, and blood-borne infection hazard to the handlers and the environment.

Assessment of anemia and iron status in a public health context

It is becoming more imperative to have methods, acceptable to the public and cost-efficient in nature, to screen populations to detect those individuals in whom iron treatment is indicated, in order to target therapy to the eligible and exclude exposure for those who do not need additional iron. The current options are to some extent both limited and problematic.

Screening with capillary blood samples

There are obvious trade-offs between costs and accuracy among the available options. The most accurate assessment of IDA includes data on hemoglobin (16) in combination with serum ferritin, transferrin receptor (TfR) plus C-reactive protein (CRP) (17), or AGP to control for inflammatory influences on serum ferritin. This “classic” set of variables can be determined in approx. 30 μL serum from capillary blood samples with satisfactory validity and precision (18–20). Although other biomarkers, such as transferrin saturation, erythrocyte protoporphyrin, reticulocyte hemoglobin content, or percentage of hypochromic red blood cells (21) could be theoretically added, the basic package offers a very reliable assessment of iron and anemia status. Financing widespread screening could be prohibitive. However, the costs of test chemicals for analysis of serum ferritin, transferrin receptor and AGP can be reduced to approx. $1 US due to miniaturization (22). In addition, cost for blood-sampling devices, transport, laboratory equipment and staff come into prominence. The risk of blood-borne diseases, like HIV and hepatitis, should not be underestimated, as single-use lancets and cannula may be used repeatedly in developing country settings. Finally, since these tests require the extraction of blood, there are associated pain (albeit minimal), even with capillary blood, and cultural taboos about blood handling; both of these consequences may induce widespread rejection by the population, especially for application to such young children.

Inspection and questionnaire approaches

IDA-assessments by clinical inspection of sclera and pale skin, assisted by a questionnaire on risk factors of iron deficiency, may be put at the other end of the scale of cost, invasiveness, reliability, and precision. The questionnaire should contain questions to assess dietary intake, socio-economic and educational status of the family in analogy to earlier guidelines of the Center of Disease Control and Prevention (23) for the US, plus some more recent risk factors (e.g., overweight) (24). Similar approaches are used in veterinary health and require well-trained health workers (25). Their advantage is that they are inexpensive and non-invasive; but their sensitivity and specificity are very limited.

Non-invasive assessment of hematological status

A first attempt to quantify hemoglobin concentration by non-invasive methods was based on back-scattered light from human tissues in vivo as determined by the Erlangen microlight-guide photometer (26). More recent technology has gained much precision. It uses orthogonal polarization spectrometry to produce an image of the sublingual microcirculation at 548 nm, which permits hemoglobin measurement in the vessels in vivo. A probe the size of a pencil is connected to a portable processing unit and produces an image that is divided into vessel and background regions. The optical density in a number of vessel seg-
ments is used to determine hemoglobin concentration (27). Estimation of the subjects’ systemic hemoglobin concentration was shown to be highly reproducible and closely correlated to conventionally determined hemoglobin concentrations in venous blood samples over a wide range of hemoglobin concentrations (28). Applicability in the field to assess the variability in a large number of subjects of different origin, however, has yet to be tested. As only about 50% of anemias in developing countries can be attributed to iron deficiency (29–31), the presence of iron deficiency needs to be established. This could be done ex post facto by measuring the response of anemia to 8 weeks of iron administration. This approach is noninvasive and promises to combine high accuracy with easy handling and low running costs beyond the expenses for the staff. Its applicability in the field, however, has yet to be tested.

**Non-invasive screening methods may offer promise**

**Slowing the rate of uptake of oral iron from supplemental forms**

Considerations to improve the safety of iron intake in malaria-endemic areas build on the observation that non-transferrin-bound iron (NTBI) activates the intracellular adhesion molecules ICAM-1, VCAM-1 and E-selectin in the vascular endothelium (32). These changes, in turn, seem to ease the adhesion of *P. falciparum* to the vascular endothelium and, thus, the prevalence for example of cerebral malaria manifesta-

tions (33). NTBI was observed to increase after pulse doses of readily available oral iron preparations (34) which are known to increase serum iron concentrations rapidly but only for comparably short periods (35). Thus, high concentration peaks of serum iron and, thus, of NTBI should be avoidable, if iron absorption were retarded.

A potential problem of oral slow release preparations for iron is that they may pass beyond the duodenum (i.e., the location of the highest iron absorption rate) before the iron is released from such galenic forms; this would impair its bioavailability and reduce its biological impact. Slow gastric delivery systems are an exception to this rule. These preparations float on the gastric juice and release their iron over an extended period of time upstream of the duodenum. This type of preparation increases iron absorption rates (36) and also avoids high peak concentrations of free iron in the intestinal lumen, which significantly reduces intestinal side effects (37). At the same time the protracted release attenuates peaks in circulating iron (BS Skikne, JD Cook, unpublished observations, 1991, quoted by Simmons et al. (37)), which is likely to reduce NTBI concentrations. This, in turn, could reduce the prevalence of cerebral malaria manifestations. Although this concept offers promise, its scientific base is not yet very solid, as field experience is lacking. According to this concept, offering iron (e.g., via a gastric delivery system or with fortified food items over the whole day) should not increase the risk of severe malaria complications.

In this context, Sprinkles, Foodlets and iron-fortified spreads should be considered to be supplements, as they deliver the iron dosage for an entire day in a single dose. Several factors seem to influence the serum iron peak with these compounds. Among them would be the dose of iron, the iron status of the child, the matrix of the supplement, and the consistency of the meal. Presumably, the peak serum concentration reached after consumption of such ready-to-eat fortificants will determine whether they are harmful in a malarial setting or not.
Another alternative to avoid hazardous peak serum concentrations of iron would be to identify and use oral iron complexes that are absorbed as such. If such complexes release their iron slowly after having been absorbed, high peak concentrations of free iron are avoided. Such approaches, however, need more developmental work before they can be used in large-scale interventions in young children.

Commentary on the wisdom and limitations of the World Health Organization

Consultancy Statement

The United Nations did not remain idly on the sidelines in the face of public health and safety consequences of the Pemba experience. In April 2006, the World Health Organization and UNICEF issued an interim statement (38), announcing the convening of an Expert Consultancy Panel, among others, to provide guidance regarding prophylactic supplementation of iron in the preschool age group. The group met in Lyon, France; a summary of this Consultancy has been released and is reprinted in this issue of the SIGHT AND LIFE Magazine (page 14–15). The considerations in this commentary provide theoretical and practical linkage to an analysis of the lessons from the Pemba trial (4). The WHO-sponsored consultancies have offered sage and sound conclusions regarding the proscription of routine iron supplementation in malaria-endemic settings.

The WHO interim statement released early in 2006 (38) is to be praised for raising notes of caution with regard to universal, saturation iron supplementation in settings with a background of HIV and/or tuberculosis (38). Moreover, the interim statement announced the drafting of a detailed research agenda as one of the main charges of the Expert Consultancy Panel. Despite the need to develop evidence to inform policy-makers on oral iron supplementation, the degree to which research protocols may be ethically challenged by the experience in Pemba cannot be overlooked. Finding a manner for inquiry that is safe for the study populations may not be easy. Independent from this issue, we touch on some gaps of knowledge below that relate to the WHO Consultancy Statement and seem to urge additional research.

During the first 6 months can be obtained from breast milk.” How such a recommendation would be operative in malarial areas falls into the large incognitos of malaria pathology and supplemental iron exposures. This theme is best viewed as a subject for research prior to implementation.

Iron status screening

Insistence on some sorting and selection of individuals for oral supplementation in malaria-endemic areas heralds a new and safer— but more complex—era of iron deficiency control. The putative clinical diagnosis of severe anemia by pallor staging mentioned here offers a low-cost, non-invasive approach with reasonable specificity but poor sensitivity. We see promise in improving the acceptability and accessibility of screening methods by use of miniaturized approaches using capillary blood (22), by non-invasive methods (27), or by well-tested approaches for IDA-assessments by clinical inspection, assisted by questionnaires on risk factors of iron deficiency. A view on cost issues, on the risk of blood-borne diseases, and on cultural acceptability seems paramount in all efforts to improve IDA assessment.

Screening to avoid iron exposure to the iron-replete has additional merits in populations that may not suffer malaria endemicity. The evidence is now convergent and virtually conclusive that iron-replete children grow more poorly when exposed to oral iron supplementation (41–43). This adds a strong rationale to consider screening before implementation of universal supplementation for pre-school-children. Finally, we underscore the need to move the proposed research agenda on routine universal iron supplementation where

Mother with anemic child

Comprehensive and effective healthcare

Healthcare measures mean to insure the public’s health, and take on special relevance where holo-endemic malaria is established. Clearly, mosquito control and avoidance of the insect vector are fundamental. Beyond such measures, exclusive breastfeeding for the first 6 months of life is explicitly recommended. Technically, the administration of micronutrient syrups, for example, is considered a violation of exclusivity of breastfeeding (39). Recently, a suggestion that there is a need for early iron supplementation in all infants has been made (40) based on the consideration that “only about 50% of their iron requirements
"other infections" are prevalent. The pathogen biology of plasmodia is not that distinct from other infections with intracellular organisms, such as leprosy, tuberculosis or HIV, so that extension of the principles of the WHO Statement (38) and Summary (44) in terms of selective coverage with iron supplementation should now be seriously considered.

Home-fortification versus fortified foods as sources of prophylactic iron

The Consultancy rightly claims lack of certainty regarding the safety of oral iron when given with food. They apply the theoretical consideration around potential adverse consequences of rapid uptake of iron into the circulation reviewed above. Supplemen tal iron in proven deficiency is to be given with food, rather than on an empty stomach. Extending this logic within the safety considerations for home fortification with iron (which is discouraged), and commercial food-fortification (which is encouraged), the admitted uncertainty takes center stage. Definitive research, rather than tentative policy guidance, is the true priority in relation to additional oral iron in the context of meals.

Proscription of folic acid supplementation and fortification

The WHO Expert Consultancy Statement contains a recommendation for the total omission of folic acid from multi-micronutrient preparations in malarial areas, including in its traditional association with iron. There is a prudent basis to omit folic acid exposure, when anti-folate metabolism is the mainstay of antimalaria therapy. However, the observation that the "widespread folate deficiency not known to be a problem in infants and young children" should not be given as a rationale to omit folic acid from preschool supplements. Folic acid should be seen as a companion hematonic nutrient to iron. Presumably, in the anticipation of a major reticuloctytic response and rapid restoration of the red cell mass enabled by adequate iron supplementation, an additional presence of folates will be needed for the proliferative response in the bone marrow.

Conclusion

Meanwhile, policy decisions and program operations that dismiss the warnings of the WHO Consultancy Statement on blanket, routine oral iron supplementation imperil the health and lives of children living within a background of chronic and recurrent malaria, in spite of good intentions. To maintain the first do no harm mandate for infant and toddler iron supplementation we need to insure a better and safer way to deliver iron in this age group. Meanwhile, we should seek creative ways to ensure that children absorb the iron that is afforded by their diet and retain the iron they absorb. For those who still show obvious clinical signs of iron deficiency, a targeted approach with supplements should be employed, preferably with galenic compositions that release as little free iron into the systemic circulation as possible. In the long run, screening for iron deficiency by innovative methods should be developed to reduce the exposure to iron for those who have no need for additional amounts of the nutrients and to satisfy the requirement of those who could benefit from repletion of their iron reserves.

References


