# Iron and Malaria Interactions: Research Needs From Basic Science to Global Policy[1,2]

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**ABSTRACT**

The resurgence in interest and concern regarding the potentially malign interactions between iron administration and malaria infections, especially in young children and pregnant women, has generated a research agenda that is both broad and deep. This paper highlights some of the key questions under 5 headings: basic science; clinical science and epidemiology; technological developments; country level planning; and global policy. At a time of unparalleled progress in basic science, which is illuminating the mechanisms by which iron interacts with infectious organisms, it is concluded that there are good medium-term prospects for achieving policy breakthroughs based on a secure foundation of disease-nutrient interactions. However, it is also stressed that there is much that can be done in the interim, especially in relation to health systems and implementation research that can empower systems to integrate iron interventions with programs for malaria prevention, surveillance, and treatment. *Adv. Nutr. 3: 583–591, 2012.*

## Introduction

The premature termination of the iron arms of the now infamous Pemba trial (1), due to an excess of serious adverse events among children receiving iron and folic acid, forced the WHO to issue new policy guidance in which the recommendation for universal iron supplementation was replaced by one advocating targeted supplementation (2). There has since been a vigorous debate about how to safely administer iron to infants, children, and pregnant women living in malaria-endemic areas (3). This has led to a policy vacuum at both the global and country levels because the proposed targeted approach is very difficult to implement and implies treatment of iron deficiency (ID) as opposed to prevention, thus putting millions of children at risk of the silent sequelae of ID. This was the background to the current symposium "Tackling Iron Deficiency and Anemia in Infants and Young Children in Malaria-Endemic Areas: Moving From Controversy Toward Guidance for Safe, Effective, and Feasible Policies and Programs" summarized in the accompanying papers (4–7). The purpose of this paper is to identify the residual research needs and make recommendations as to their prioritization given the urgency with which we need to surmount the policy stasis imposed by the Pemba results. Although further research on iron–malaria interactions is urgently required and will undoubtedly inform the policy agenda, some elements of it will inevitably take several or many years to mature, and this should not be allowed to inhibit interventions against ID designed against the background of our current, albeit inadequate, knowledge. The final paper of this symposium addresses that challenge (8).

The research needs, listed in **Table 1**, are summarized under 5 headings: basic science; clinical science and epidemiology; technological developments; country level planning; and global policy. The table represents an executive summary so readers are encouraged to view the table before continuing. The needs identified represent the views of the authors and should not necessarily be interpreted as the collective view of the symposium participants.

## Basic science

If we assume a high probability of some malign interactions between exogenous iron administration and pathogenicity of infections, it is essential that the basic science investigating the potential mechanisms is used to inform

**Table 1.** A summary of research needs ranging from basic science to global policy[1]

| Research need | Practical implications | Likely time to interventions |
|---|---|---|
| **Basic science** | | |
| Mechanisms of iron–malaria interactions | Will inform optimization of iron interventions: chemical composition, dose, timing, fortification vs. supplementation, etc. | Short to medium |
|   Hepatic and/or blood stage effects? | | |
|   Acute (e.g., NTBI) and/or chronic (e.g., iron loading) effects? | | |
|   Systemic and/or enteric effects? | | |
| Mechanisms of iron interactions with other pathogens | Will fill extensive knowledge gaps relevant to design of iron-related therapeutic (e.g., iron withholding) and preventive interventions | Medium to long |
|   Malaria-associated bacteremias | | |
|   Iron-dependent bacteria (especially TB) | | |
|   Iron-dependent viral infections (e.g., HIV, hepatitis C) | | |
| Hepcidin–iron axis as a mediator of immune responses | Possibility of using hepcidin agonists or antagonists as therapeutic agents and/or vaccine adjuvants | Medium to long |
|   Hepcidin as component of innate immunity | | |
|   Hepcidin–iron axis as potential modulator of adaptive immune responses, especially vis-à-vis vaccines | | |
| Biology of iron acquisition in an infectious environment | Should definitions of ID and anemia cutoffs be modified in infectious environments? | Short to medium |
|   Is ID and/or anemia partly an adaptive response to infectious threats? | Must infections be reduced *before* tackling ID? | |
|   Are there windows of opportunity for safe iron acquisition between intercurrent infections? | | |
| **Clinical science and epidemiology** | | |
| Risks vs. benefits | Necessary to balance iron aversion and policy stasis created by Pemba results. Reminder that most interventions (especially vaccines) have risks. Balanced judgment required | Short |
|   Health metrics research on pros and cons of iron interventions | | |
|   Further research on iron, brain development, and cognition | | |
| Establishing safe modes of iron administration | The ethics Catch-22 (see text) will prevent any new trials in high-risk environments without malaria surveillance and control. Small trials can never cancel out Pemba | Probably never |
|   Very large-scale trials to test safety of iron in malarial regions (theoretical need but not feasible in practice to assess serious adverse outcomes and mortality) | | |
|   Can only be assessed against nominal proxy outcomes such as malarial infection, NTBI, altered microbiota | | |
| Screening | Good clinical practice recommends assessment and diagnosis of a condition before intervention. Pemba data show this to be critical and WHO adopted a screening resolution, but is it practicable? | Short to medium |
|   Is the Pemba substudy conclusion that iron is safe in children with ID secure? Requires replication. | | |
|   Is the risk vs. benefit equation dependent on markers of ID? | | |
|   Would screening ever be a practical option? | | |
|   Screening implies treatment; is this desirable? | | |
| Supplements vs. fortifiers vs. foods | Research in these domains will likely yield the most immediate benefits and help fill the policy/practice void | Immediate and onward |
|   Wide research agenda exists regarding the efficacy and safety of supplements vs. fortifiers | | |
|   Iron as part of multinutrient packages for home-based fortification (powders or lipid-based pastes) are currently the favored options but still require validation | | |
|   Food-based solutions are recognized as difficult to achieve at present (but see below) | | |
| Life-course approaches | May direct interventions away from pregnancy and young childhood when iron–malaria interactions are most damaging | Short |
|   Can a life-course approach (e.g., enhancing iron status of mothers-to-be, cord clamping) reduce the need to intervene in infancy? | | |
| **Technological developments** | | |
| Formulation of supplements and fortifiers | Much research already completed, but new basic science findings can inform further optimization | Immediate and onward |
|   Further optimization of chemical composition, dose level, mode of administration, etc.,. | Efficacy and tolerability (low side-effect profile) tends to correlate with cost; breaking this relationship is critical for low-income settings | |
|   Controlled slow release in duodenum and less residual unabsorbed iron for intestinal microbiota is the challenge | | |
| Crop technology | Can staple foods with enriched iron content (e.g., BioCassava Plus) help bridge the growing gap between flesh food supply and demand ? | Medium and long term |
|   Accelerated transgenic crop enhancement programs | | |
| Point-of care diagnostics | Inexpensive, simple, and reliable point-of-care tests will be required if a screening approach is to be endorsed. Even if not endorsed diagnosis of ID is clearly important in tropical medicine | Immediate and onward |
|   Design, optimization, testing, and production of very low cost point-of-care tests for iron deficiency | | |

*(Continued)*

**Table 1.** (*Continued*)

| Research need | Practical implications | Likely time to interventions |
|---|---|---|
| Country level planning | | |
|   Endemicity of malaria and ID | Governments can make better plans for iron | Immediate and onward |
|     Map regions where malaria and ID overlap | interventions and avoid inaction in nonmalarial | |
|     Understand modifying factors such as altitude, season | areas | |
|   Integration of programs | Potential adverse reactions can be avoided if | Immediate and onward |
|     How best to integrate intermittent preventive therapy, bed nets, and iron? | interventions against malaria either precede or accompany iron interventions | |
| Global policy | | |
|   Assessing risks vs. benefits | Necessary to balance iron aversion and policy stasis | Short |
|     See above | created by Pemba results. Reminder that most interventions (especially vaccines) have risks. Balanced judgment required | |
|   Universal vs. targeted approaches | Resolution and guidance required on whether to | Short |
|     See above | adopt screening and a targeted approach to combating ID in malarial areas | |
|   Global trends in malaria | Important to keep iron–malaria issue in an appropriate | Immediate and onward |
|     Monitor global trends in malaria | perspective against rapidly changing patterns of | |
|     Monitor trends in prevention, surveillance, and treatment | disease | |

[1] ID, iron deficiency; NTBI, nontransferrin-bound iron.

the design of clinical and epidemiological studies. These should have appropriate endpoints and sufficient power to investigate differential effects between subpopulations or environmental interactions. This is particularly important considering the ethical impossibility of conducting another Pemba-type study.

## Mechanisms of iron–malaria interactions

*Blood or liver stage effects?* Does iron promote plasmodial infection via effects on the liver stage or blood stage or both? Because erythrocytes are packed with iron and present the parasite with the challenge of detoxifying the iron as hemazoin, many observers find it hard to envisage that ID could limit blood stage development and hence that supplementation would augment blood stage virulence, although it cannot be ruled out. In contrast, soon after this symposium, Portugal et al. (9) reported compelling evidence, at least in mice, that hepcidin-mediated iron redistribution from hepatocytes to macrophages in mice carrying a blood stage parasitemia prevented secondary infection by sporozoites (so-called superinfection) by starving the exoerythrocytic forms of iron (see references 5 and 10 for abbreviated summaries of these extensive experiments and for discussions of their implications). This work firmly establishes the iron–hepcidin axis as an arm of innate immunity and paves the way for numerous follow-up studies; for instance, to establish how this protection is altered by giving exogenous iron. It also confirms a key role for the iron-regulatory hormone hepcidin, which may emerge as a superior biomarker for iron status (see the following) and which will undoubtedly be the target of extensive clinical and molecular research as we further interrogate its biology.

*Acute and/or chronic effects of iron?* In the post-Pemba search for possible explanatory mechanisms, much attention has focused on the possibility that the unphysiologically large bolus dose of iron, especially when given between meals as recommended to avoid food-based iron chelators, could overwhelm the capacity of transferrin to remove it safely from the basolateral membranes of enterocytes. This might lead to a transient peak of nontransferrin-bound iron (NTBI), a possibility discussed in some detail by Dewey and Baldiviez (7) in the accompanying paper. NTBI could lead to oxidant damage and/or ready availability of iron to plasmodial parasites and/or provision of substrate for iron-seeking bacteria. The last of these might be a special concern given that bacteremias are common comorbid conditions in malaria (11,12) and may have led to the serious adverse outcomes in Pemba (1). Given the high level of malaria transmission in Pemba at this time, chronic asymptomatic malaria would have been prevalent and the occurrence of fever triggering attendance at a health facility may have been the result of superimposed bacterial or viral infections rather than a direct result of the malaria infection. Several ongoing studies are attempting to address the issues surrounding NTBI, the measurement of which poses significant technical challenges with skepticism surrounding the validity of some methods.

An alternative interpretation of the mechanism of iron toxicity is that it results from a gradual iron accumulation and is more likely to occur in iron-replete children. Both of these possibilities are supported by analysis of the Pemba data: first, time-to-event plots for adverse outcomes in the iron- and noniron-receiving arms only started to diverge after $\sim$ 200 d of supplementation and, second, in the substudy, supplementary iron was beneficial to iron-deficient children and only harmful to those who were iron replete at baseline (13).

Distinguishing between acute and chronic toxicity of iron, if indeed there is a clear distinction, would be enormously helpful in designing optimal iron protocols.

*Systemic and/or enteric effects?* The questions posed above all relate to potential systemic effects of orally administered iron. It is also possible that iron could have profound effects on the microbiota of the gut as most enteric bacteria require iron. Interestingly, the bifidobacteria have a low iron need and breast milk is low in iron and keeps it tightly bound to lactoferrin, for which there are specific receptors that allow efficient uptake of what little iron is present. Recently, Zimmermann et al. (14) showed that relatively low levels of iron given in fortified biscuits to children in Cote d'Ivoire alter the microbiota in an unfavorable direction and result in elevated levels of fecal calprotectin, a marker of gut inflammation. This raises several further research questions: Could the enteric inflammation occasionally disrupt the barrier function of the gut to such an extent that it allows bacterial translocation leading to septicemia? Will lower doses of oral iron minimize these effects on the microbiota? If so, what are the lowest doses that will retain efficacy against ID? Can iron formulations be designed that optimize duodenal iron uptake to such an extent that there is insufficient residual iron entering the lower gut to disrupt the normal flora?

## Mechanisms of iron interactions with other pathogens

Although not directly related to the issue of iron–malaria interactions, the issues that have been placed in such sharp focus by the Pemba trial are already stimulating a renewed interest and numerous research programs into the possible effects of iron on susceptibility to other pathogens. Important new findings are likely to emerge within the next 5 y. In this respect, it should be remembered that the conclusion that the adverse events noted in Pemba were due to interactions between iron and malaria is based almost solely on an indirect inference drawn from the fact that there is no malaria in the region of Nepal where a parallel trial found no overall adverse effects. It should also be noted that the Nepal trial did not have a substudy to determine whether there might have been opposite effects by initial iron status, as suggested in the Pemba trial. Thus, iron interactions with other infections may be highly pertinent.

*Iron-dependent bacterial infections.* A broad range of bacteria are highly iron-dependent and possess iron-response elements that modify their gene expression to cope with a varying iron supply. Many have captured specialist iron-ac quisition apparatus from other bacteria to be able to colonize low iron niches (such as the systemic circulation of humans). Often these genes are concentrated in the genomic regions associated with high pathogenicity and hence show evidence of the centrality of iron to host-pathogen competition for a nutritional resource (15). To the best of our current knowledge, these attributes are not shared by any other nutrient, and hence it makes sense to concentrate our research efforts in this direction until we better understand the biology of these interactions.

To take a single prominent example, *Mycobacterium tuberculosis*, the causative organism for tuberculosis, is highly iron dependent. It has long been suspected that iron administration can exacerbate tuberculosis and accelerate mortality (16,17), and the molecular and genomic mechanisms underpinning the host-pathogen battle for iron are now starting to become clearer (18). Emerging data not yet in the public domain are starting to point to a (potentially critical) role for hepcidin in mediating some of these effects (H. Drakesmith, personal communication).

There is a series of clear, although very challenging, research questions in relation to iron and bacterial infections (in addition to those previously listed vis-à-vis the potential effects of NTBI and gut damage), among which are the following: Which bacteria are especially sensitive to host iron supply and, given that some can strip iron even when tightly bound to host transporters, how does iron status and oral iron administration affect bacterial survival, growth, and virulence? How does the malaria-induced diversion of iron from the systemic circulation and hepatocytes into macrophages (via hepcidin up-regulation) affect host susceptibility to bacterial infection (and in particular to intracellular organisms such as *Mycobacteria* and *Salmonella* that colonize the macrophage)? What implications do these biological mechanisms have for strategies to combat ID in environments where infections are still prevalent? Can manipulation of host iron status, by means of iron chelators and/or hepcidin agonists or antagonists, be used therapeutically to inhibit bacterial growth and allow host adaptive immunity to complete the task of elimination?

*Iron-sensitive viral infections.* In an analogous manner to bacteria, there is strong evidence that many viral infections are iron dependent (19) and that the course of infections, including HIV, may be accelerated by high iron status and exogenous iron administration (16). Emerging evidence again implicates a role for hepcidin in mediating a novel iron-dependent arm of the innate immune system (20). These early hints challenge us with a similar set of research questions for viruses as set out for bacteria.

## The hepcidin–iron axis as a mediator of immune responses

Reference has already been made to some of the emerging evidence that the hepcidin–iron axis constitutes a newly discovered arm of the innate immune system (9,20,21). In some senses, this merely confirms all of the preexisting evidence, some of it known for more than half a century, that iron redistribution resulting in the systemic hypoferremia of the acute phase response is a beneficial anti-infective process (15). But, what is so exciting about the rapidly emerging hepcidin story is that it opens windows into the functioning of a series of black boxes that have hitherto concealed their biological secrets. Once we understand the molecular cogs, gears, and linkages, the sensors and effectors, that control iron homeostasis in the face of an infectious threat, then they will be amenable to therapeutic interventions based either on pharmacological interventions or, in the context of Third World health, on a better understanding of when to administer (or withhold) iron, how, how much, and to whom. It is a reasonable prediction that hepcidin research

will have clarified many of our current iron and infection imponderables within a decade from now.

## Biology of iron acquisition in an infectious environment

The elements, discussed previously, of the interactions between host iron status and infections coalesce into an interesting question that is considered heretical by public health interventionists, namely, is ID, and the consequent anemia, adaptive in the sense that it has optimized survival in highly infectious environments? This highly plausible thesis that receives repeated, although by no means unanimous, observational support (22–24) is worthy of further research because, if true, it lays out a clear pathway for interventions; we must reduce the threat of infections before we can optimize cognitive function and physical performance by raising iron status to levels above those that have existed at least for the past 10,000 y in most population groups. The imperative of coordinating iron interventions with malaria protection policies has been repeatedly emphasized in this symposium (4,8). This call should be extended to all infections.

A second question about the biology of iron in unhygienic environments is this: Are there windows of opportunity for safe iron acquisition between intercurrent infections, and, if so, can we design intervention strategies to work in harmony with this natural biology? Emerging evidence strongly supports the view that hepcidin responds to an infectious threat within minutes or hours to lock out exogenous iron (via down-regulation of the iron efflux protein ferroportin on enterocytes) (25) and lock down body iron (via an analogous effect in the macrophage) (25). Evidence from recently treated malaria patients also indicates that hepcidin decreases rapidly when the infectious threat has passed (much more rapidly than C-reactive protein and ferritin, for instance) and hence reopens pathways for iron absorption and redistribution to the erythron, allowing rapid recovery of iron equilibrium and hemoglobin levels (26). What are the public health implications of this biology? There may be long windows and short windows. Long windows would typically be associated with seasons. Our research in rural Gambia reveals a strong seasonality of most infections including malaria (highest in and shortly after the rains), and hence an appropriate strategy might be to concentrate on building up iron stores during the low-infection dry season (but note that if high iron status per se makes individuals more susceptible to infection, this may not be a desirable course to take). Short windows may last only days or weeks. To capitalize on opportunities to boost iron status during these windows, we would need a point-of-care diagnostic that rapidly registered readiness to receive supplemental iron. Hepcidin appears to have the necessary attributes to become such a marker.

## Clinical science and epidemiology
### Estimating risks versus benefits of iron interventions

Almost all health interventions carry some risks. This is certainly true of most drugs and vaccines. Preclinical animal studies and phase I trials explore mechanisms, establish optimal dose levels likely to maximize benefit while minimizing risk, and test for grossly overt adverse reactions. Phase II and III trials scale the studies up to better estimate levels of risk and benefit, which are then reported to licensing authorities, and, if approved, the interventions are introduced into medical practice. Postmarketing surveillance is then used to audit rare adverse outcomes that might not have been seen even in large phase III trials, and many compounds are withdrawn at this stage. The problem with iron interventions is that they have been used for decades without any such trials. When they have been tested, the outcome was almost always hemoglobin level and/or anemia rates. Other outcomes such as cognition, immune function, and human capital endowment were rarely assessed. Therefore, when the worrying outcome of Pemba emerged, it focused minds almost entirely on the negative attributes of iron. During the Lyons Consultancy held by WHO (2), a plea was made for health metrics research that would allow a balanced appraisal of the pros and cons of iron interventions. That call has not been adequately met and represents an important outstanding research need.

Such analysis requires more secure input data on the consequences of ID and on the potential advantages of reversing it. Further research on iron, brain development, and cognition is especially needed.

## Establishing safe modes of iron administration

The current mindset in the field is that intravenous iron is definitely contraindicated in malarial areas and that iron tablets and syrups represent a highly unphysiological means of administering iron that may lead to pathology (as discussed previously). As discussed by Dewey and Baldiviez (7) in this symposium, food fortification, either centrally or at point of consumption via Sprinkles or lipid-based nutrient supplements, is currently favored, but is it safe? Dewey and Baldiviez list the emerging data and conclude that

> Results from 6 home fortification studies in malaria-endemic areas (some not yet published) showed no increased risk of adverse effects. Most of these studies, however, had small to moderate sample sizes, so severe adverse events could not be adequately assessed. There is also a lack of information on the potential modifying effect of initial iron status on treatment effects. Although the evidence to date suggests that home fortification with iron in malaria-endemic areas is safe, additional research would be valuable.

> However, it is very challenging, if not impossible, to obtain conclusive evidence on the safety of home fortification in malaria-endemic areas. Severe adverse events associated with iron consumption are likely only seen where infectious disease control is lacking, yet it would be unethical in this type of setting to conduct studies without providing any services to monitor and treat infectious disease, including malaria. A huge sample size would be required to rule out a modest increase in severe adverse effects (7).

This neatly articulates the Catch-22 faced by investigators. There seems no ethical way around this, and, therefore,

although replication or refutation of the Pemba results would be extremely valuable, it will never be forthcoming and future actions must be designed against this constraint.

An alternative approach is to assess iron interventions against a panel of known or suspected adverse outcomes that may lie on a pathway to serious adverse events and death. The present panel of proxy outcomes includes malaria infection and parasitemia rates (including placental infection), NTBI levels, alterations in gut microbiota, markers of gut inflammation, growth retardation, and, in sufficiently large trials, other clinical outcomes such as bacteremias and hospitalizations. It is hoped that the basic science research into mechanisms summarized previously may point to other intermediate proxies of possible harm.

### Is screening for ID a realistic option?

The statement arising from the WHO Lyon Consultancy advocated that in malaria-endemic areas, iron should only be administered to children shown to be iron deficient on screening (2). This symposium revealed ambivalence on this matter. Crowley et al. (6) were asked to summarize the current prospects for field-friendly methods for such screening, yet other papers implicitly concluded that screening is not really a practical option because a) it would be too costly and complicated to administer within the sorts of health systems where the need is greatest and b) by definition, screening implies treatment as opposed to prevention and may leave millions of children vulnerable to the debilitating effects of ID.

Another problem is that, although the Pemba substudy very clearly demonstrated that the harmful effects of iron were limited to children who were iron replete (as judged by having zinc protoporphyrin levels <80 $\mu$mol/mol hemoglobin) (1,13), another study from Tanzania has yielded an apparently opposite effect in a trial using a multiple micronutrient intervention that contained iron (27). The latter trial assessed ID/sufficiency according to serum ferritin levels, which could contribute to the apparent conflict. Clearly, this is an issue that needs to be resolved. Basic science findings might help here. The former result (i.e., that iron-replete children show adverse effects) is consonant with the chronic iron-loading mechanism. The latter result is consonant with the acute NTBI-type mechanism because intestinal iron absorption is up-regulated in iron-deficient children and may facilitate a greater uptake of nonphysiological unchelated iron.

Assuming that screening for ID is an effective tool (and, irrespective of Pemba results, good clinical practice favors treatments based on a clear diagnosis), then the practicalities of this need to be evaluated in real-life settings together with a cost–benefit analysis. The stakes are high because the costs are measured in children's lives rather than the costs of treatment because iron is very inexpensive.

### Supplements vs. fortifiers vs. foods

There is a large and important research agenda to define the optimal mode of administering iron to poor populations. Some key issues are listed in the Table 1 but are not discussed further in this paper as they have been extensively covered in the accompanying paper by Dewey and Baldiviez (7).

### Life-course approaches

Can a life-course approach (e.g., enhancing iron status of mothers-to-be, cord clamping) reduce the need to intervene in pregnancy and infancy? Certainly there is evidence that each of these interventions can have an impact on iron status (28,29), but trials have not yet been published that report results from a truly integrated life-course approach. One element that would need to be considered is that even preconception iron administration might increase the chances of a mother having malaria in pregnancy if the overall iron status is a determinant of risk, as is currently thought to be the case (5,24).

## Technological developments

### Formulation of supplements and fortifiers

A very wide range of compounds are already used as iron supplements or fortifiers, yet development of new compounds still progresses in the search for the optimal compromise between efficacy, side-effect profile, and cost. The issue of cost is particularly important in the developing country context under consideration here, and, unfortunately, there tends to be a reciprocal relationship between cost and optimal efficacy and side-effect profile. The side effects of iron compounds (such as constipation, black stools, gastrointestinal discomfort, dizziness) are much more significant than they might at first appear because, together with the absence of any obvious therapeutic benefit to the patient, they are responsible for very low levels of long-term compliance with standard iron-folate formulations offered to pregnant women.

Note that safety is not included among the triangulation points listed for optimization of iron compounds. This is because (with the exception of intravenous iron administration, which has been known for some decades to exacerbate malaria) before Pemba, most compounds were assumed to be safe. The Pemba trial has changed this, and the observations of Zimmermann et al. (14) that even modest levels of fortifying iron can induce gut inflammation (14) complicate the picture still further. In the past, one strategy to combat low absorption was simply to give more iron, but this is no longer an acceptable response. As discussed previously, the strategy now being used by many is to minimize the amount of iron given. This drives a need for higher absorption rates to maintain efficacy, and this represents an important research need. Good examples of the necessary studies were published recently (30–32) and already indicate that, for instance, 3 mg of iron as iron EDTA may have similar efficacy to 12.5 mg of iron as iron sulfate and might thus reduce residual iron for the microbiota.

### Crop technology

It is recognized that the costs and relative scarcity of flesh foods and other sources of highly bioavailable iron put

them beyond the reach of many poor people much of the time (33). Accelerated transgenic crop enhancement programs offer one route to try to overcome this roadblock and are receiving appropriate funding from the Bill and Melinda Gates Foundation and other funding bodies as well as from the private sector. The research needs range from the initial genetic engineering to produce high iron varieties, through field trials of yields, to consumer trials of acceptability, efficacy trials, investigations of social marketing strategies to enhance take-up, and, finally, large-scale effectiveness monitoring. With such a large agenda, it will be some years before a major impact can be made, and in the meantime, chemical fortification represents a much simpler route.

## Point-of-care diagnostics

An ability to make a rapid and secure diagnosis of ID at the primary health care level would represent a major step forward, irrespective of whether future policy encompasses the screening option. Graded dipstick and paper-based tests are available for many analytes and for diagnosis of several conditions. A decade ago, malaria dipsticks were newly on the market, yet WHO recently evaluated no fewer than 41 brands, indicating the pace at which technological developments can occur. In the accompanying paper, Crowley et al. (6) discuss the current state-of-play regarding field assessment of tools for ID. Their paper focuses mostly on field-friendly transdermal methods for assessing hemoglobin because no other methods are yet available for testing. Attempts to develop a field-friendly transdermal fluorescence–based method for assessing zinc protoprophyrin are in progress, and such an instrument would be a significant step forward if it proves robust, reliable, and very low cost.

Other initiatives, driven in particular by the Bill and Melinda Gates Foundation's Biomarkers of Nutrition for Development program through National Institute of Child Health and Human Development/NIH, are in progress to improve community-level screening for iron status (34). These are concentrating significant investment on the issue of how to adjust survey data on ferritin to compensate for high levels of inflammation, a procedure applicable to survey data but not viable for individual patient assessment in which low ferritin will always have high specificity but very low sensitivity.

Our group has early data indicating that hepcidin has the potential to form the basis of an excellent point-of-care diagnostic to indicate safe and ready to receive iron, especially now that effective antibody-based assays have been developed (the absence of which delayed progress in the field for several years). There is a compelling logic to the use of hepcidin because it is the key iron-regulatory hormone that integrates signals from transferrin saturation, hypoxia, hepatic iron, inflammation, and infection and is both a sensor of iron status and an effector of iron absorption and distribution (21). We believe that this sets out an important research need with excellent prospects for success in the

development of new tools both for individual clinical diagnosis of ID and for population screening. Appropriate cutoffs must be evaluated and then transferred to affordable tests such as those being developed for paper-based diagnostics.

## Country-level planning

This symposium was organized by the Micronutrient Initiative in response to the frustrations voiced by many country-level planners and policymakers regarding what they see as a void in the guidance from international bodies (4). In fact, there is plenty of enabling research that countries can be doing to circumvent the perceived policy stasis.

## Mapping endemicity of malaria and ID

*Map regions where malaria and ID overlap.* Most countries have varied topography that affects disease transmission (especially infections such malaria and helminths that affect ID) and diet. Likewise, regional differences in poverty and the health and transportation infrastructure will affect access to health services. Regional differences in malaria transmission are not always predictable (35) and hence require country-specific data. Health departments can perform basic surveys to map out the areas in which ID and malaria overlap to the greatest extent. A partial example is provided in Table 2, which lists anemia rates (assessed by Hemocue) identified in a nationwide survey of The Gambia conducted by the National Nutrition Agency (36). The survey was integrated with a parallel survey of vitamin A deficiency but, in this case, did not simultaneously assess malaria rates in the same samples. The survey clearly identifies where interventions are most required and in this setting because malaria is highly seasonal, offers at least a partial solution to the iron–malaria conundrum if the optimal solution of minimizing malarial transmission cannot yet be attained, namely, to attack the problem in the dry season and in the most needy areas.

*Understand modifying factors such as altitude and season.* As implied in the example given above, health departments could refine their intervention policies if they have a clear understanding of the factors such as altitude,

**Table 2.** Example of within-country regional differences in anemia rates[1,2]

| Division (geographic area) | Prevalence of anemia in children (1–5 y) | |
| --- | --- | --- |
| | Moderate (%) | Severe (%) |
| Banjul (urban) | 31 | 6 |
| Kanifing (urban) | 74 | 3 |
| Western (rural coastal) | 66 | 9 |
| Central River (rural) | 77 | 17 |
| Lower River (rural) | 22 | 20 |
| North Bank (rural) | 32 | 12 |
| Upper River (rural) | 87 | 35 |

[1] Moderate deficiency = hemoglobin <110 g/L; severe deficiency = hemoglobin <70 g/L.
[2] Reproduced from Reference 36 with permission.

water sources, vegetation, season, and regional food supplies that affect the prevalence of both ID and malaria. This represents a primary research need for any countries for which such knowledge is not yet secure.

### Integration of programs
*How best to integrate intermittent preventive therapy, bed nets, insecticides, and iron.* Almost all of the research needs outlined above would be made redundant if malaria could be eradicated. This is not yet attainable, but it is possible for countries to develop integrated approaches that combine antimalarial interventions such as intermittent preventive therapy, insecticide-treated bed nets, indoor residual spraying, and availability of malaria treatment regimens at the village level with administration of iron interventions. Many countries, often with the support of international bodies, are testing such programs with a view to scaling them up. This seems the most viable and desirable of all routes forward at the current time [see also the observations of Stoltzfus (8) in the accompanying paper].

### Global policy research needs
Many of the research needs already outlined, for example, the health metrics research into costs versus benefits of iron programs and the issue of universal versus targeted approaches, are relevant to global policy. A final significant issue relates to how the iron–malaria problem may evolve in the future.

### Global trends in malaria
*Monitor trends in prevention, surveillance, treatment, and global trends in malaria.* The good news on the horizon is that malaria rates have recently decreased very markedly in several countries in sub-Saharan Africa (37,38). The precise causes of these decreases and whether they will be sustained in the future remain to be evaluated, but the trends provide some real grounds for optimism, and further and wider monitoring of these trends will help inform future policy options. Such monitoring and the subsequent collation of such data at the country, regional, and global levels by WHO therefore represent another important research goal.

### Conclusions
The Pemba trial has become a nemesis in the minds of many health interventionists and has certainly created a most undesirable policy paralysis that, among many other counterefforts, has stimulated the present symposium. From a research standpoint, however, it has proved to be a very powerful wake-up call and has stimulated an unprecedented resurgence in efforts to better understand the highly complex interactions between iron and malaria (and other microorganisms). This resurgence has coincided with a decade in which our knowledge of the molecular pathways regulating iron metabolism has exploded and in which a key central regulator of iron metabolism, hepcidin, was discovered. The basic sciences are therefore in a very strong

position to grapple with the issues. Pemba has also been beneficial in attracting research funding to the field, and there are many ongoing studies focusing on iron–malaria interactions, most notably through the Iron and Malaria program managed by National Institute of Child Health and Human Development/NIH with substantial funding from the Bill and Melinda Gates Foundation. Pemba has also been helpful from a research standpoint in reestablishing an ethical equipoise that once again makes it possible to conduct randomized, controlled trials using placebo arms without iron; in fact, it is now regrettably more difficult to include iron than to exclude it in some settings.

Research will ultimately clear the murky windows through which we are trying to see our way to formulating policy, but until such a time, the current imperative at the country level is to progress with action. The most logical course is to prioritize programs for malaria reduction and treatment and then to join these with iron programs, the options for which have been set out in some of the accompanying papers (5,8).

### Literature Cited
1. Sazawal S, Black RE, Ramsan M, Chwaya HM, Stoltzfus RJ, Dutta A, Dhingra U, Kabole I, Deb S, Othman MK, et al. 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. Lancet. 2006;367:133–43.
2. World Health Organization. Conclusions and recommendations of the WHO Consultation on prevention and control of iron deficiency in infants and young children in malaria-endemic areas. Food Nutr Bull. 2007;28:S621–7.
3. Prentice AM. Iron metabolism, malaria, and other infections: what is all the fuss about? J Nutr. 2008;138:2537–41.
4. Harding KB, Neufeld LM. Iron deficiency control for infants and young children in malaria-endemic areas: a call to action and consensus among the research community. Adv Nutr. 2012; 3:551–4.
5. Spottiswoode N, Fried M, Drakesmith A, Duffy PE. Implications of malaria on iron-deficiency control strategies. Adv Nutr. 2012; 3: 570–8.
6. Crowley C, Solomons NW, Schümann K. Targeted provision of iron: The evolution of a practical screening option. Adv Nutr. 2012; 3:560–9.
7. Dewey KG, Baldiviez L. Safety of universal provision of iron through home-fortification of complementary foods in malarial areas. Adv Nutr. 2012; 3:555–9.
8. Stoltzfus RJ. Iron and malaria interactions: programmatic ways forward. Adv Nutr. 2012; 3:579–82.
9. Portugal S, Carret C, Recker M, Armitage AE, Gonçalves LA, Epiphanio S, Sullivan D, Roy C, Newbold CI, Drakesmith H, et al. Host-mediated regulation of superinfection in malaria. Nat Med. 2011;17:732–7.
10. Prentice AM. Hepcidin and iron-mediated resistance to malaria. EMBO Mol Med. 2011;3:620–2.
11. Mabey DC, Brown A, Greenwood BM. Plasmodium falciparum malaria and Salmonella infections in Gambian children. J Infect Dis. 1987;155:1319–21.

12. Were T, Davenport GC, Hittner JB, Ouma C, Vulule JM, Ong'echa JM, Perkins DJ. Bacteremia in Kenyan children presenting with malaria. J Clin Microbiol. 2011;49:671–6.

13. Stoltzfus RJ, Heidkamp R, Kenkel D, Habicht JP. Iron supplementation of young children: learning from the new evidence. Food Nutr Bull. 2007; 28(4, Suppl)S572–84.

14. Zimmermann MB, Chassard C, Rohner F, N'goran EK, Nindjin C, Dostal A, Utzinger J, Ghattas H, Lacroix C, Hurrell RF. The effects of iron fortification on the gut microbiota in African children: a randomized controlled trial in Cote d'Ivoire. Am J Clin Nutr. 2010;92:1406–15.

15. Prentice AM, Ghattas H, Cox SE. Host-pathogen interactions: can micronutrients tip the balance? J Nutr. 2007;137:1334–7.

16. McDermid JM, Prentice AM. Iron and infection: effects of host iron status and the iron-regulatory genes haptoglobin and NRAMP1 (SLC11A1) on host-pathogen interactions in tuberculosis and HIV. Clin Sci (Lond). 2006;110:503–24.

17. Schaible UE, Kaufmann SH. Iron and microbial infection. Nat Rev Microbiol. 2004;2:946–53.

18. Andrews NC. Forging a field: the golden age of iron biology. Blood. 2008;112:219–30.

19. Drakesmith H, Prentice A. Viral infection and iron metabolism. Nat Rev Microbiol. 2008;6:541–52.

20. Armitage AE, Eddowes LA, Gileadi U, Cole S, Spottiswoode N, Selvakumar TA, Ho L-P, Townsend ARM, Drakesmith H. Hepcidin regulation by innate immune and infectious stimuli. Blood. 2011;118:4129–39.

21. Ganz T. Hepcidin and iron regulation, 10 years later. Blood. 2011;117:4425–33.

22. Weinberg ED. Iron depletion: a defense against intracellular infection and neoplasia. Life Sci. 1992;50:1289–97.

23. Wander K, Shell-Duncan B, McDade TW. Evaluation of iron deficiency as a nutritional adaptation to infectious disease: an evolutionary medicine perspective. Am J Hum Biol. 2009;21:172–9.

24. Senga EL, Harper G, Koshy G, Kazembe PN, Brabin BJ. Reduced risk for placental malaria in iron deficient women. Malar J. 2011;10:47.

25. Nemeth E, Tuttle MS, Powelson J, Vaughn MB, Donovan A, Ward DM, Ganz T, Kaplan J. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. Science. 2004;306:2090–3.

26. Prentice AM, Doherty CP, Abrams SA, Cox SE, Atkinson SH, Verhoef H, Armitage AE, Drakesmith H. Hepcidin is the major predictor of erythrocyte iron incorporation in anemic African children. Blood. 2012;119:1922–8.

27. Veenemans J, Milligan P, Prentice AM, Schouten LRA, Inja N, van der Heijden AC, de Boer LCC, Jansen EJS, Koopmans AE, Enthoven WTM, et al. Effect of supplementation with zinc and other micronutrients on malaria in Tanzanian children: a randomised trial. PLoS Med. 2011;8:e1001125.

28. Gulati R, Bailey R, Prentice AM, Brabin BJ, Owens S. Haematological effects of multimicronutrient supplementation in non-pregnant Gambian women. Eur J Clin Nutr. 2009;63:970–7.

29. Chaparro CM, Neufeld LM, Tena Alavez G, Eguia-Líz Cedillo R, Dewey KG. Effect of timing of umbilical cord clamping on iron status in Mexican infants: a randomised controlled trial. Lancet. 2006;367:1997–2004.

30. Troesch B, Egli I, Zeder C, Hurrell RF, de Pee S, Zimmermann MB. Optimization of a phytase-containing micronutrient powder with low amounts of highly bioavailable iron for in-home fortification of complementary foods. Am J Clin Nutr. 2009;89:539–44.

31. Verhoef H, Veenemans J. Safety of iron-fortified foods in malaria-endemic areas. Am J Clin Nutr. 2009;89:1949–50.

32. Hurrell R. Iron and malaria: absorption, efficacy and safety. Int J Vitam Nutr Res. 2010;80:279–92.

33. Raiten DJ, Namasté S, Brabin B. Considerations for the safe and effective use of iron Interventions in areas of malaria burden–executive summary. Int J Vitam Nutr Res. 2011;81:57–771.

34. Raiten DJ, Namasté S, Brabin B, Combs G, Jr., L'abbe MR, Wasantwisut E, Darnton-Hill I. Executive summary–biomarkers of nutrition for development: building a consensus. Am J Clin Nutr. 2011;94:633S–50S.

35. Okiro EA, Alegana VA, Noor AM, Mutheu JJ, Juma E, Snow RW. Malaria paediatric hospitalization between 1999 and 2008 across Kenya. BMC Med. 2009;7:75.

36. National Nutrition Agency/MRC. Nationwide survey of anemia and vitamin A deficiency. NaNA/MRC. 2001.

37. Ceesay SJ, Casals-Pascual C, Erskine J, Anya SE, Duah NO, Fulford AJ, Sesay SS, Abubakar I, Dunyo S, Sey O, et al. Changes in malaria indices between 1999 and 2007 in The Gambia: a retrospective analysis. Lancet. 2008;372:1545–54.

38. Okiro EA, Hay SI, Gikandi PW, Sharif SK, Noor AM, Peshu N, Marsh K, Snow RW. The decline in paediatric malaria admissions on the coast of Kenya. Malar J. 2007;6:151.