Research Needed to Strengthen Science and Programs for the Control of Iron Deficiency and Its Consequences in Young Children\textsuperscript{1–3}

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Abstract
The purpose of this article is to highlight critical research needs for the effective prevention and control of iron deficiency and its consequences in children living in low-income countries. Four types of research are highlighted: The first involves scaling up interventions that we know are effective, namely iron supplementation of pregnant women, delayed cord clamping at delivery, immediate and exclusive breast-feeding, and continued exclusive breast-feeding for 6 mo. The second entails evaluation research of alternative interventions that are likely to work, to find the most cost-effective strategies for a given social, economic, and epidemiological context. This research is especially needed to expand the implementation of appropriate complementary feeding interventions. In this area, research needs to be designed to provide causal evidence, to measure cost-effectiveness, and to measure potential effect modifiers. The third is efficacy research to discover promising practices where we lack proven interventions. Examples include how to detect infants younger than 6 mo who are at high risk of iron deficiency, efficacious and safe interventions for those young high-risk infants, and best protocols for the treatment of severe anemia. The fourth includes basic research to elucidate physiological processes and mechanisms underlying the risks and benefits of supplemental iron for children exposed to infectious diseases, especially malaria. Strategic research in all 4 areas will ensure that interventions to control pediatric iron deficiency are integrated into national programs and global initiatives to make pregnancy safer, reduce newborn deaths, and promote child development, health, and survival. J. Nutr. 138: 2542–2546, 2008.

Introduction
This symposium takes place at a critical time for those striving to improve child nutrition, and iron deficiency in particular. The scientific literature on pediatric iron deficiency is long-standing and vast. Nonetheless, we find ourselves debating issues in the field of pediatric iron nutrition that are both old and newly challenging. The purpose of this article is to highlight critical research needs for the effective prevention and control of iron deficiency and its consequences in children living in low-income countries.

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\textsuperscript{3} Author’s own estimations based on $a = 0.05, b = 0.20$, event rates observed in recent trial in Zanzibar, and effect sizes of 20 g/L for hemoglobin and 10\% changes in hospitalization or mortality. These are expressed as orders of magnitude for illustrative purposes only.

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transmission experienced higher rates of hospitalization and mortality if they received universal daily low-dose iron and folic acid supplements (compared with placebo) (8) confirms that even low-dose supplements, under some conditions, can increase risk of severe infectious disease. Thus, although prevention or treatment of iron deficiency in young children improves their developmental potential and, at least in some circumstances, decreases their risk of severe disease, iron supplementation of children who are not deficient is risky, at least in some contexts. Experts convened by WHO have judged the risk to be associated with context of malaria transmission and have stated that where young children are at high risk of malaria transmission, iron supplements should not be given universally but rather should be targeted to children with iron deficiency (9). This and other key points from the WHO statement are summarized in Figure 1.

The broad array of partial knowledge and unanswered questions requires a variety of types of research. We need to act on what we know while we continue to discover new answers. And, given the present urgency of childhood malnutrition in the global health and development arena, we must ask research questions and design research studies in ways that make them most immediately relevant to programmatic action. This article suggests a framework for conceptualizing and organizing our research agenda.

**Scaling up what works: iron supplements for pregnant women, immediate and exclusive breast-feeding, and delayed cord clamping**

Several interventions that prevent iron deficiency in young children have well-established efficacy and are advocated for immediate and large-scale programmatic action based on evidence reviews (10). In these cases, we know what to do, but we are still learning how to do it. The research agenda should address questions of how to create effective programs that can reach large numbers of people in various health systems contexts with the greatest cost-effectiveness (5). Given the weak health systems that exist in many communities and countries with high burdens of pediatric iron deficiency, this research must identify key health systems’ assets and constraints and must propose means to build capacity and to overcome or work around constraints.

Research on scaling up is needed for provision of iron supplements to pregnant women (with folic acid or in a multiple-micronutrient supplement), delayed clamping of the umbilical cord at birth, immediate exclusive breast-feeding within the first hour of birth, and continued exclusive breast-feeding for ~6 mo. Regarding exclusive breast-feeding, although feeding infants with iron-fortified formula is associated with high iron stores, formula feeding is not recommended for most infants, especially in low-income countries, which are the focus of this symposium. Where formula is not widely available or is often not used properly, infants who are exclusively breast-fed have better iron status than those who are breast-fed but not exclusively (11,12). See the article by Dr. Chaparro in this symposium (13).

Although the focus of this article is pediatric iron deficiency, note that several of these interventions confer important health benefits in addition to the prevention of iron deficiency. For example, provision of iron supplements to pregnant women also improves maternal health and survival, and immediate and exclusive breast-feeding also prevents diarrheal disease and improves neonatal and infant survival (10,14).

This type of research has been variously named implementation research or delivery sciences. The research methods are largely from the social sciences, although implementation research must remain keenly focused on the established pathways of biological efficacy. There is no benefit to making something "work at scale" if an essential element of its efficacy has been lost.

The neonatal health agenda provides some useful models for nutrition and iron deficiency in particular. Neonatal health programs in low-income settings face a gap between discovery of efficacious interventions and large-scale implementation that is similar to that for nutrition programs (14). Furthermore, key nutrition interventions (e.g., cord clamping and immediate and exclusive breast-feeding) should be part of the package of neonatal services. We can learn from the ways that neonatal health researchers have worked to define packages of interventions that are likely to be feasible in different health systems contexts (15) and have designed randomized effectiveness trials to evaluate the costs and effectiveness of their delivery under various implementation models (16). Scaling up proven interventions to prevent pediatric iron deficiency in low-income countries will require similar research strategies.

**Evaluation of alternative interventions that are likely to work: complementary feeding**

A major focus of research on pediatric iron deficiency has been and should continue to be the issue of appropriate complementary feeding of infants from ~6 mo to 24 mo, as infants transition from a diet of solely breast milk to a mixed diet of breast milk plus other foods. It is during this age period that iron deficiency becomes most prevalent and severe. And, although it is true that an infant’s risk of iron deficiency at this critical age window is conditioned by prior events (birth weight, maternal iron status, cord-clamping practices, and exclusivity of breast-feeding), it is also true that these antecedent risk factors are almost universally compounded by a diet that is low in bioavailable iron. There are 2 levels of questions: questions specific to iron (how much, what form, how often?) and questions about how to incorporate iron recommendations into a more holistic infant nutrition program.

When it comes to complementary feeding interventions to prevent iron deficiency, there are many interventions that have worked in past research studies or programs and that might work in a particular future situation. But the social, economic, and other contextual factors may be too complex for us to predict with certainty a single best strategy for a given setting—certainly not for all the low-income countries. For example, liquid iron supplements (17), home fortificants (18,19), fortified cereal blends (20), and lipid-based spreads (21) have all been successful in efficacy trials or programs. These products are promoted and targeted through specific messages that situate the product vis-a-vis-
vis local traditions, specify usage times per day or per week, clearly identify the intended age range of the child, and make appropriate claims about the health benefits. Finally, these products may be distributed through social programs that provide the product free or that use cash transfers or that rely on the free market with or without social marketing.

Although questions of dose and form of iron (e.g., ferrous sulfate vs. iron-sodium EDTA) and local feasibility and acceptability (what product do households prefer) may be answerable through formative research including small randomized trials, ascertaining the best combination of product, message, and delivery strategy can only be answered with research designs that approach programmatic realities or that evaluate the strategy (or strategies) in action in a real program. Furthermore, complementary feeding is important not only for iron nutrition, but also for other key micro- and macronutrients, and the current political prioritization of complementary feeding interventions is because of its combined benefits to child growth, development, health, and survival. Programmatically relevant research in this area will need to be designed to address the broad array of interests and outcomes, which include but are not limited to iron deficiency.

Five aspects of appropriate research design on complementary feeding should be highlighted. First, research should be designed to provide the strongest causal evidence that is appropriate and possible. Randomized comparisons provide the gold standard of evidence and should be employed where possible, but they are impossible or inappropriate in some political contexts, for example, if the government has already enacted certain policies. Quasiexperimental designs using randomized time delays or nonrandomized comparisons can also provide strong evidence (22,23).

Second, careful thought is needed in selecting the outcomes for evaluation. Obviously, we are interested in iron status and iron-deficiency anemia. However, the interventions of interest have multiple outcomes, including status of other nutrients, growth, activity patterns, appetite, motor and cognitive development, morbidity, and mortality. Increasingly, as nutrition and health agendas become better integrated, policy makers need to weigh interventions in terms of their multiple outcomes, and we miss opportunities if we focus too narrowly on the status of a single nutrient or even solely on nutrition rather than broader health outcomes. Realistically, the choice of outcome measure is also driven by feasibility and resources. For example, consider the following orders of magnitude of sample size: to compare 2 groups with iron status as outcome will require 100–200 children per group, to compare hospitalization rates requires on the order of 10,000 child-y of observation, and to compare mortality rates requires on the order of 100,000 child-y of observation (2).

Third, research should be designed to measure the costs of those benefits. Cost-effectiveness analyses have become an essential part of health planning because they provide a rational basis for choosing among intervention options and programmatic strategies for delivering them (24). Such analyses are strongest when they are embedded prospectively in intervention research, rather than being considered post hoc. The CHOICE (Choosing Interventions that are Cost-Effective) website (25) of WHO is 1 resource for planning and interpreting cost and cost-effectiveness data.

Fourth, research should be designed to explain how the benefits were obtained. This seems obvious, but in reality, interventions involve multiple parts and multiple pathways—both intended and unintended—that might influence outcomes. For example, in a complementary feeding intervention that uses a home fortificant, the outcome of growth could be affected through the nutrients in the fortificant, changes in infant feeding practices brought about by educational messages and heightened attention to infant feeding, better access to health care services during the evaluation, or concurrent changes in morbidity that might or might not have been caused by the intervention. A randomized design may allow causal inference, but randomization on its own does not unpack the black box of how the outcomes were changed. In designs that do not use randomization, the causal inference depends on establishing plausible pathways of effect (23). Understanding how an intervention worked requires research methods designed for that purpose, broadly termed process evaluation (26). Good examples in the literature include studies of infant feeding education in Peru (27), or the multicountry evaluation of the Integrated Management of Childhood Illness (28).

Fifth, research should be designed to illuminate who benefited most, who least, and who not at all. Benefit from an intervention is never uniform, and learning about this variation in benefit is necessary to generate hypotheses about the underlying biology and also to increase the accuracy when we generalize from a limited number of studies. There is a growing body of evidence supporting the notion that the effects of iron interventions differ qualitatively depending on the iron status of the individual. The most dramatic example comes from the Pemba, Zanzibar trial in which children with iron deficiency (elevated erythrocyte protoporphyrin) benefited greatly from iron plus folic acid supplements (risk of hospitalization or mortality was reduced by 38%, P = 0.02), but children who had normal values of the same markers at baseline appeared to be harmed (same risk was increased by 63%, P = 0.24) (8). The value of intervention research can be greatly increased if careful thought is devoted to which potential predictors of harm or benefit should be measured. Characterizing baseline iron status is essential.

Efficacy trials to test interventions where appropriate actions are still unclear: iron interventions for high-risk infants younger than 6 mo; treatment of severe anemia Several critical issues remain where we are not sure of the right interventions to address specific issues related to iron deficiency. One question is how to identify those infants who will become significantly iron deficient before 6 mo, the age at which we would normally target supplements, home fortificants, or iron-fortified complementary foods. Risk factors for iron deficiency in the first half of infancy include maternal iron deficiency, low birth weight, immediate cord clamping, and inappropriately early introduction of solid foods or cow’s milk (13). The recommendation to provide iron supplements to low-birth-weight infants starting after 2 mo of age is longstanding (7), but feasible protocols have not been developed to identify the infants who would truly benefit. Furthermore, the safest and most beneficial dose and duration of supplementation have not been evaluated.

Surprisingly, the appropriate use of iron in the treatment of severe anemia is also an unresolved issue. The prevalence of severe anemia in young children may exceed 20% in environments where malaria is common (29) and is recognized to be multifactorial in origin (30). How should these children be treated? Randomized treatment trials in Africa have compared various regimens in which iron was not used at all (31), equal iron was used in all treatment arms (32), iron was used for 14 d vs. 3 mo and the longer duration was more beneficial (33), or a large dose of iron (200 mg daily) was compared with no iron and was associated with no benefit but more nonmalarial illness (34).
Currently, WHO and UNICEF recommend iron and folic acid supplementation along with treatment for malaria and helminths (the latter if the child is older than 2 y) (7), but these recommendations have not been rigorously evaluated.

**Basic research to elucidate mechanisms**

In addition to intervention research, more basic research is also needed, especially to further our understanding of the interactions between iron status and infections. Our knowledge of iron status and child development has been substantially advanced through a concerted research agenda that has included animal models, clinical research in humans, and epidemiological research, including randomized trials and prospective cohort studies (35). In contrast, our knowledge about iron and infection is lacking in critical ways. Many questions have been raised by the striking findings from the Pemba trial that iron plus folic acid supplements were associated with greater severe morbidity overall, and in the substudy that iron plus folic acid supplements strongly benefited iron-deficient children but appeared to harm those who were not iron deficient. A very similar concurrent trial in Nepal found no benefit and no risk to child morbidity or mortality from iron plus folic acid supplementation (36). In an attempt to interpret those findings for programs and policy, expert consensus was based on 3 interpretive assumptions: the findings of harm were conditioned on high malaria transmission, that the harm and benefit were attributable to the iron in the supplement and not the folic acid, and that the most likely mechanism is that the highly soluble form of iron in the supplement led to a postdose surge in nontransferrin-bound iron that was accessible to the malaria parasite. Although these have been necessary and useful judgments, we should remember that none of them can be substantiated by the evidence at hand. A concerted research agenda using animal models and both fundamental and human metabolic research is needed to increase our understanding.

**Summary and conclusions**

A spectrum of research is needed to advance the control of pediatric iron deficiency in low-income countries, including large-scale implementation research, effectiveness evaluations, cost-effectiveness research, process evaluation of interventions in programmatic settings, efficacy trials, and more fundamental research. Interventions to control iron deficiency in young children are relevant to several global health goals and initiatives, including making pregnancy safer, improving neonatal health and survival, as well as child development, health, and survival. A strategic research agenda will strengthen the evidence base for these interventions and at the same time demonstrate ways to identify and overcome barriers to their large-scale implementation. Such an agenda will require a variety of research methods, the results of which are mutually informative and reinforcing.

Other articles in this supplement include references (13,35,37,38).

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