HarvestPlus Position Paper

Iron and malaria: addressing potential risks from food-based approaches to alleviate iron deficiency among children less than two years of age exposed to malaria

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PROLOGUE: THE ETHICAL CONTEXT

Given the fact that HarvestPlus is involved in research aimed to help poor and nutritionally deficient people, it is of utmost importance that HarvestPlus does not cause unnecessary and/or avoidable harm to those individuals involved in research, does not hide relevant concerns to those involved, and engages in careful consideration of potential harm and ethical dilemmas. A principal role of the HarvestPlus Program Advisory Committee (PAC) is to define a set of guiding principles for research and communication, ensuring the lines of authority between governance and management are not crossed.

The goal of this document is to address concerns about the potential risks of biofortification and develop a consensus statement concerning policy recommendations.

BACKGROUND

Approximately 47 percent of the world's children less than five years of age are anemic (WHO 2008). Iron deficiency also constitutes an important global economic constraint, despite the fact that there are efficacious and, in some cases, effective nutrition and public health interventions with high returns on expenditures (Horton, 2008). In the case of iron-deficiency control, it has been strongly suggested that there is no need for major investment in new industrially fortified or supplementation products, but rather that resources should be applied to solving the primary bottleneck in achieving progress: the lack of effective delivery systems for the interventions at hand. Biofortification is not among the mainstream interventions discussed, but it will also have to deal with drop uptake and dissemination issues of its own. However, the fact remains that only in very few instances have results from research on iron-deficiency control interventions been translated to "effective and sustainable programmatic action and to understanding large-scale implementation and cost-effectiveness" (Stoltzfus, 2008). Much more emphasis on the effectiveness and safety of interventions to control and prevent iron

deficiency is needed. HarvestPlus shares this global mandate with other organizations dedicated to vitamin and mineral deficiency control and prevention.

In this context, the interaction between iron, nutrition, and infection acquires great relevance, as the potential danger of increased risk of infections as a consequence of having too much iron is clear and present. This has been highlighted by a recent, large randomized preventive iron-and-folic acid (IFA) supplementation trial with infants and young children living in almost constant exposure to high malaria transmission rates in the Tanzanian island of Pemba. Since low dose (12 mg) iron supplements given to iron replete infants and young children caused increased morbidity and mortality in this environment, any intervention that seeks to increase iron intake in a comparable context, be it by means of food or other vehicles, must do so with all due diligence, poignantly aware and responsive to the potential risks and benefits involved given the circumstances that surround those whose health and well-being we intend to improve.

WHAT DO WE KNOW ABOUT THE SAFETY OF NUTRITIONAL IRON INTERVENTIONS FOR INFANTS AND YOUNG CHILDREN?

Iron supplementation and adverse health events in malarious regions

Previous literature on the health effects of iron supplementation in malarious regions has shown conflicting results (Oppenheimer 2001, Gera 2002, Desai 2003, Verhoef 2003, Verhoef 2002, Berger 2000, Mebrahtu 2002). Recent evidence from preventive iron and folic acid supplementation trials in Pemba and Nepal has raised concerns regarding the safety of iron supplementation among young children. The Pemba and Nepal studies are the two largest preventive trials undertaken to date to test the efficacy and safety of supplementation. Both were randomized trials designed to assess mortality effects. The Nepal study found no effect of supplementation on mortality or serious adverse events. In the Pemba trial, a 16 percent (0.92-1.47) higher risk of mortality was observed among children supplemented with iron-folic acid (IFA) as compared to placebo (Sazawal, 2006). Combined iron groups supplemented with IFA (with or without zinc) showed a 12 percent higher risk of serious adverse events (hospitalizations due to serious illnesses/mortality) as compared to the placebo group. The IFA treatment group also had a significant 16 percent (CI: 0-32%) rise in malarial illnesses and 32 percent (95% CI: 2-70%) excess risk of severe malarial illnesses as compared to placebo group. There was an increase in risk of serious respiratory infections, a part of which may have been contributed by underlying consequences of malaria (Snow, 1997).

More recently a Cochrane meta-analysis on "Oral iron supplementation for preventing or treating anemia among children in malaria-endemic areas" provides a comprehensive review of randomized-controlled trials on this topic (Ojuwku et al.

2009). The authors conclude that "iron does not increase the risk of clinical malaria or death, when regular malaria surveillance and treatment services are provided. There is no need to screen for anemia prior to iron supplementation." Similarly in the sub-study of the Pemba trial, iron-deficient children who were under an active malaria detection program experienced a significant 38 percent reduction (p=0.02) in the rate of adverse events. In anemic children, the rates were reduced even farther, by 41 percent (p=0.02) as compared to placebo.

Oral iron supplements and intravenous iron infusions have been associated with increased placental malaria. In a retrospective study from Papua New Guinea, malaria prevalence rose only in primiparous women who were treated with intravenous iron (Oppenheimer 1986). Peripheral or placental parasite density did not increase among Gambian multigravidae on oral iron supplements who participated in a randomized placebo-controlled study (Menendez 1994). In another retrospective study in pregnant Thai women taking iron supplements to treat anemia, the risk of *Plasmodium vivax* but not *Plasmodium falciparum* malaria increased during prospective follow-up (Friedman 2009). Because of key differences in study populations (i.e. gravidity, baseline iron status) and other potential confounders (i.e. route, dosage, and timing of supplementation) these studies have not resolved whether antenatal iron supplementation increases pregnancy malaria risk.

Iron-fortified foods and infectious morbidity

A recent review of evidence to this effect seems to exonerate iron as found in foods (industrially or traditionally processed) from potential harm to children and infants irrespective of their iron status (Dewey 2007). Most of the iron-fortified vehicles in these studies decreased the prevalence of anemia, and two studies produced significant negative effects, i.e. increased morbidity or decreased growth (Table 1). Admittedly, however, there is no direct evidence from randomized clinical trials conducted in populations where malaria is hyperendemic, and this is an area where further research might be warranted. The issue has been summarized by Professor K. Dewey as follows:

> *Low intake of bioavailable iron from complementary foods is the major cause of the high prevalence of iron deficiency anemia among children 6 to 24 months of age in developing countries…No adverse effects of increasing iron intake through fortification or home fortification of complementary foods have been reported, but large-scale studies that include sufficient numbers of iron-replete children are lacking. Further research is needed to verify the safety of iron-fortification strategies, particularly in malarial areas. (Dewey K, 2007*).

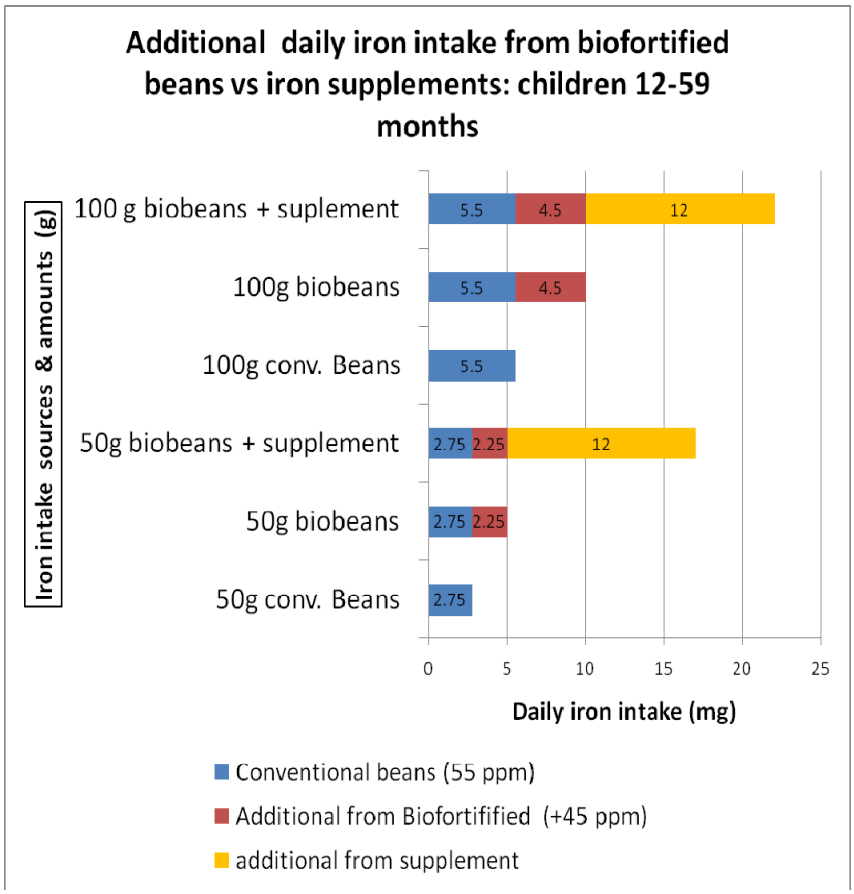
Table 1. Randomized controlled trials on the safety of iron-fortified foods using growth and morbidity as indicators of risk

Study and intervention type	Country	Comparison group	Effect on growth	Effect on morbidity	Effect on anemia
CENTRALLY FORTIFIED FOODS					
Javaid, 1991	Pakistan	Unfortified cereal	Increased Weight gain	NS but lower diarrhea	Increased Hb & ferritin
Walter, 1993	Chile	Unfortified cereal	NS	NS	Decreased anemia
Schumann, 2005	Guatemala	Unfortified beans	n/a	NS	Hb increase in iron deficient subjects
Lartey, 1999	Ghana	Unfortified maize-legume blend	NS	NS	Lower prevalence of iron deficiency
Rivera, 2004	Mexico	Unfortified cereal	NS	n/a	Decreased anemia
Faber, 2005	South Africa	No intervention	Increased	n/a	Decreased anemia
Sazawal, 2007	India	Unfortified milk	Increased	Decreased	n/a
SPRINKLES (multiple micronutrients including iron)					
Zlotkin, 2001	Ghana	$FeSO_4$ drops	NS	NS	NS (equally efficacious)
Zlotkin, 2003	Ghana	Zinc gluconate	NS	NS	Decreased anemia
Christofides, 2006	Ghana	$FeSO_4$ drops	n/a	Decreased	NS (equally efficacious)
Christofides, 2005	Canada	Placebo	NS	n/a	NS*
Sharieff, 2006a	Pakistan	Placebo	n/a	NS	NS
Sharieff, 2006b	China	No intervention	NS	NS	Increased serum ferritin in daily Sprinkles group
Giovannini, 2006	Cambodia	Placebo	NS	NS	Decreased anemia
FOODLET (multiple micronutrients including iron)					
Smuts, 2005	South Africa	Placebo	NS	NS	Increased serum ferritin in iron and daily groups
Adu-Afarwuah, 2006	Ghana	Not randomized no intervention group	NS	NS	n/a
NUTRIBUTTER (multiple micronutrients including iron)					
Adu-Afarwuah, 2006	Ghana	Not randomized no intervention group	Increased growth and Improved motor milestones	NS	n/a

NS= not significant; n/a = not assessed
Source: Modified from Dewey K. Food Nutr Bull, 2007;28(4):S595.
*54% compliance in treatment group.

For purposes of comparison, the estimated increase in iron intake from biofortified beans (dry/raw weight) for children 12–59 months of age is shown in the chart below. An average daily intake (50 g raw beans = 125 g cooked/drained beans) of conventional beans with ~55 ppm of iron and negligible iron losses during processing will provide ~2.75 mg iron, whereas 50 g of biofortified beans (~100 ppm) will contribute around 5.5 mg to daily iron intake. At a very high intake level for a

five year old child weighing 20 kg (~120 grams raw beans = 300 g cooked beans), biofortified beans could provide 12 mg iron/meal. This iron dose should be examined in light of different dietary intake guidelines for iron for this (presumably iron replete) age group: the safe upper level of intake (UL, 40 mg), the RDA (7-11mg)[1], and the estimated average requirement (EAR, 3-6.9 mg)[1]. With the important reservation in mind that these dietary guidelines were developed using data from non-malarious populations, we estimate that when added to a 12 mg iron supplement, this amount of food iron would result in iron intake at about half the UL. On the other hand, if the mechanism(s) responsible for iron-related morbidity pertain to absorbed iron effects, the potential risk associated with bean iron would practically evanesce among children with respect to iron supplements, given the relatively small amount of food intake by children 6–24 months and the dampening of iron absorption produced by most staple food crops in general.



[1] The lower value corresponds to the recommendation for children 7–12 months and the higher figure for 1–3 year old children to an average gastric capacity of ~ 15 g/kg body weight. For diets with low mineral bioavailability, the recommended dietary intake (RNI) has been set at 11.6 mg

The World Health Organization's recommendations: Based on the evidence summarized above, the ad hoc WHO consultative group (2007) recommended against universal iron supplementation for children under five years of age in malaria-endemic regions. Iron therapy should be provided after screening to iron-deficient children, though the current recommendation of universal supplementation still holds for children in non-malarious regions. WHO also recommended more research on possible strategies for providing iron in safe ways so as to avoid possible toxic effects. Nonetheless, iron-fortified foods were considered safe and recommended as the preventive alternative of choice, irrespective of the epidemiology of malaria.

Despite said recommendations, the dilemma remains for institutions responsible for iron interventions research in developing countries. Usually it takes biologically implausibility or randomized trial evidence for a conclusion to be clearly well-founded in scientific facts and logical reasoning. In the case of food iron interventions and malaria, we have neither of those elements. What we have is an expert judgment endorsed by UNICEF and WHO on the one hand, and a public health ethical issue on the other.

The ad hoc technical advisory group to the National Institutes of Health on this topic (2008-9) concluded similarly that

> *The evidence with specific regard to the impact of providing iron under conditions of malaria and a high infective load remains unanswered and warrants a focused research effort. At this time, the provision of iron via tablets or liquids requires caution and may be the least desirable approach in malaria-endemic areas. The Technical Working Group (TWG) concluded that fortified foods may be the most viable alternative intervention, and could include iron fortification of complementary foods for infants and young children and iron-fortified staple foods and condiments for women and older children. The TWG emphasized the need for careful selection of the iron compound and the amount added. If done correctly, iron-fortified foods can be designed as a sustainable intervention to improve or maintain the iron status of all at-risk population groups.*

Biofortification was defined by the TWG as a "potential future strategy" to combat iron deficiency but not discussed.

Thus, the expert consensus regarding iron supplementation can be summarized in the following terms:

- Iron supplementation prevents nutritional iron-deficiency in children and pregnant women.
- Iron supplementation in the form of syrup or tables has negative effects on iron-replete children in areas where malaria transmission is high.

- Children in the same area who are iron-deficient will benefit from supplementation.
- Iron supplementation to children in such areas should, therefore, only take place on the basis of diagnosed iron deficiency or in combination with effective disease control strategies (diagnosis of iron deficiency depends on the availability, affordability, and feasibility of suitable screening methods in such populations).
- Iron supplementation may also increase malaria susceptibility in pregnant women.

Widely shared views among scientists who have stated their view about iron fortification are that:

- The mostly likely explanation of the negative effects of iron supplementation has to do with the dose, timing, and form in which the iron is given.
- One should not expect similar negative effects from fortified (including biofortified) foods.
- However, there is a lack of evidence of these views based on randomized trials.

HarvestPlus is faced with a case of scientific uncertainty and with a number of inferences but no hard evidence in the form of results from randomized trials. The combination of this uncertainty, as it relates to human health, has the potential to lead to controversy and uncontrolled public reactions. If the experts are wrong, there could be negative consequences for women and children.

THE PUBLIC HEALTH ETHICS OF IRON INTERVENTIONS

Minimal risk as an ethical threshold for research upon children

There are at least two discussions to be had here. First, there is a discussion about the relative weight of the principle of beneficence (B) and the principle of non–maleficence (NM). It can be seen that in many situations, we seem to give priority to NM against B. This may be explained in light of what is called the acts and omission doctrine (AO), according to which it is worse to do something bad than it is to abstain from doing an equivalent amount of good. This may sound plausible if the "bads" are highly negative and the "goods" are luxuries. However, in the present case, the "bads" and the "goods" are very much the same (avoiding disease/death). In this situation, agreement is unlikely. Some people will say that B and NM should be given equal weight, whereas others will insist that NM should still be given priority. Second, there is a discussion about the so-called precautionary principle (PP). This principle may be understood given that NM has priority, but this is not

the only way to understand it. Fears of scientific presumption could also be seen as underlying PP.

Policy options for iron interventions in malaria-endemic populations[2]

Whether or not to endorse iron-biofortified foods is a decision that is often discussed in the context of anemia prevention, maternal mortality reduction, cognitive development, and work capacity improvement. From a scientific point of view, this may be wise since the evidence for the protecting effect of iron on such functional consequences of iron deficiency is, for the most part, the best type of evidence possible. However, from a public health point of view, one needs to bear in mind that the impact of a higher or unnecessary iron intake might affect the frequency of other adverse conditions as well. Apart from protective effects, adverse effects need to be taken into account.

Policymaking in public health often requires the balancing of pros and cons. As an example of the pros of iron deficiency anemia (IDA) eradication, it has been estimated that IDA causes 591,000 perinatal deaths and 115,000 maternal deaths globally every year. The associated loss of healthy life years amounts to more than 19 million disability-adjusted life years (DALYs) from perinatal causes and more than 3 million DALYs from maternal causes. When the direct sequelae of iron deficiency anemia are added, the total global burden attributed to iron deficiency anemia amounts to 841,000 deaths and 35 million DALYs.

The benefits of IDA control and the functional consequences of iron deficiency need to be balanced against all other potential risks and benefits. For drugs and potentially toxic nutrients, the likelihood of curing one disease usually needs to be balanced against the risk of know or unknown side effects. This needs to be made more explicit in political and societal debate. From a normative point of view, it is obvious that public health authorities should do good and follow the beneficence principle, but the difficulty for policymakers is that they have to balance the certainty of benefits to an, as yet, unknown amount of risk to harm. Thus, the non-maleficence principle leads to reticence to move forward.

The precautionary principle, therefore, leads to two opposite consequences: (1) avoiding potential harm of a biofortification (fortification or supplementation) with iron as initiated by governments but also (2) avoiding the fact that many people ingest adequate amounts of iron, so that many women reach pregnancy with adequate iron stores, many children are born healthy, and working adults lead more economically productive lives. The debate is even more complex. For some of the

[2] Adapted from M. C. Cornel, D. J. de Smit, and L. T. W. de Jong-van den Berg. 2005. Folic acid—the scientific debate as a base for public health policy. *Reproductive Toxicology* 20 (3): 411–415.

impact on public health, there is type-A evidence, and for some other impacts, we have to rely on a lower level of evidence.

A third ethical principle, autonomy, also needs to be discussed in this context. A government policy to fortify or endorse fortification implies a decision taken for an entire population without asking for individual decisionmaking and informed consent. One should consider that public health decisions demand a different ethical balancing of pros and cons than individual health care. To maximize social utility, preventive interventions that are very effective and efficient need to be selected. Whether informed decisionmaking is possible or not will vary depending on the strategy of implementation. For example, if there are biofortified and conventional bean or pearl millet varieties in the market, then labeling the products should allow consumers to make their own choices. However, prohibiting food fortification does not contribute to autonomy.

For any public health decision on fortification with iron to be made, we suggest that all available evidence be taken into account. For those potential effects (either protective or adverse) where evidence is lacking or of observational quality, definitive studies need to be performed, as they already are under guidance from the NIH/WHO consortium (http://www.nih.gov/news/health/mar2008/nichd-05.htm), to get the answers as soon as possible. For example, affordable methodologies to screen children for iron deficiency in order to target iron interventions more effectively and safely in scenarios with different prevalence levels of anemia and malaria and to determine the balance between the number of adverse health events avoided among iron-deficient subjects who receive the intervention adjusting for coverage of and compliance with malaria prophylaxis are needed.

The bottom line regarding evidence about the risks associated with iron interventions in malaria-endemic countries can be summarized by paraphrasing a personal communication from Dr. Rebecca Stoltzfus on this matter. Basically, we have two choices. One, we can agree with the expert judgment, which is controversial, and forge ahead with interventions for iron-fortified weaning foods. If we move ahead in this way, it would be prudent to make sure that such programs are preceded by randomized clinical trials and, if evidence so warrants, that scale-up dissemination takes place under careful monitoring and enhanced malaria prophylaxis and treatment. Or two, we can choose not to use the most promising intervention (i.e. iron-fortified weaning foods) to prevent IDA in children in high malaria transmission areas because its safety is not "non-controversial." In doing so, we prioritize safety (which may seem laudable), but we also risk giving up the potential to do a great deal of good for many children. Undeniably, between these two approaches there lies a great deal of ground for thoughtful, context-specific choices.

Therefore, during program implementation, surveillance systems become vital to vulnerable populations as they enable program managers to study and opportunely respond to: the frequencies of severe anemia cases; maternal mortality associated with anemia; school attendance and success rates; low birth weight prevalence; malaria prophylaxis and treatment coverage and compliance; bean variety coverage and consumption; malaria prevalence; hospitalizations of children. Hence, it will be our policy to conduct iron intervention research prior to varietal release of biofortified crops and only within the context of functional surveillance systems that effectively track key outcome indicators that can be used for periodic assessment and corrective programmatic action. We will also make scientific evidence, including meta-analysis and technology assessments, available to public health authorities in charge of decisionmaking and program management, and we will work collaboratively to strengthen existing health care delivery systems inasmuch as resources permit.

It will be our policy to work in concert with malaria prevention, such that the benefits of the intervention and the monitoring of key outcomes can be shared between malaria and nutrition programs and proper corrective actions can be implemented in a timely manner. Malaria experts, in general, are very committed to the reduction of anemia in children, and there is substantial evidence that iron interventions will help all of us meet that goal. Especially given the controversies, it is important to have local malaria programs working with nutrition interventions and not in isolation to them, politically speaking. So, this means that we will avoid working where malaria programs are weak or absent (as in Pemba during the trial mentioned previously) and also where malaria programs are opposed to our intervention due to the controversy. Conversely, we will endeavor to work in areas where malaria programs are relatively strong and where the leaders of those programs are open to collaboration on the joint monitoring of anemia and clinical malaria outcomes.

NEXT STEPS

Based on the ethical considerations outlined above and having scored favorably in other areas such as moral significance (are the benefits achieved of same moral order as potential risks?), fairness (do beneficiaries and those running the risk belong to the same group of people), and transparency (is the issue communicated in an open way?), it is determined that HarvestPlus should be focusing its next steps on issues of:

1) autonomy (have the affected persons been informed and do they have a choice?) and

2) responsibility (is enough done to investigate risks and consider alternatives?)

On issues of autonomy, the HarvestPlus PAC Iron-and-Malaria Subcommittee agrees that it does not seem feasible to label high-iron crops so as to give consumers a choice, but it is possible is to involve local stakeholders, such as community representatives, NARs, health authorities, local medical organizations and others, in consultation. On issues of responsibility (due diligence), the subcommittee explored various strategies and agreed to focus on: (1) following closely the developments on malaria and iron issues without getting involved in risk research, (2) partner with third parties studying risk, and (3) conduct risk research which piggybacks on in-house nutritional research to get a better grasp of the issues and thereby improve the quality of the program's science.

POLICY CONSEQUENCES FOR HARVESTPLUS—THE CONSENSUS VIEW

- To deal with issues of autonomy, HarvestPlus undertakes consultations with NARS and other community representatives before handing over high iron crops in areas with high levels of malaria.
- The consultations should present the ethical discussion and the relevant scientific findings on the basis of which HarvestPlus has decided to move on with iron biofortification in areas with malaria.
- Plans to roll out high-iron beans in Africa and pearl millet in India should not be delayed but will be informed by studies which conduct an appraisal of known and hypothetical interventions like iron supplementation taking into account infections and malaria in the areas these crops will be grown and eaten.
- HarvestPlus will:
    1. Closely and proactively follow the development of this area of knowledge in expert discussions about iron and malaria;
    2. Partner with third parties studying risk;
    3. Conduct in-house risk research which piggybacks on nutritional research;
    4. If possible, set up retrospective studies of the relationship between food iron intake and malaria; and
    5. Dissuade the indiscriminate use of additional non-food iron interventions where baseline food iron intake has been increased by the introduction of iron-biofortified crops resulting in a lower threshold for risk of adverse effects associated with excess iron intake among iron-replete children and other vulnerable groups.

REFERENCES

Berger, J., J. L. Dyck, P. Galan, A. Aplogan, D. Schneider, P. Traissac, and S. Hercberg. 2000. Effect of daily old Togolese children. *European Journal of Clinical Nutrition*. 54 (1): 29–35.

Black, R. E., A. H. Lindsay, Z. A. Bhutta, L. C. Caulfield, M. Onis, M. Ezzati, C. Mathers, and J. Rivera. 2008. Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet* 371 (9608): 243–260.

Bogdan, C. 2001. Nitric oxide and the regulation of gene expression. *Trends in Cell Biology* 11 (2): 66–75.

Brunet, L. R. 2001. Nitric Oxide in parasitic infections. *International Immunopharmacology* 1 (8): 1457–1467.

Carnap, R. 1950. *Logical foundations of probability.* Chicago, I.L.: University of Chicago Press.

Clark, W. C. 1980. Witches; Floods and Wonder Drugs: Historical Perspectives on Risk Management. *In societal risk assessment: how safe is safe enough?* ed. R. G. Schwing and W. A. Albers, Jr. New York: Plenum Press.

Copenhagen Consensus Center. 2008. Copenhagen consensus 2008 results. http://www.copenhagenconsensus.com/Default.aspx?ID=953; 2008. Accessed 2010.

Domellof, M., K. G. Dewey, R. J. Cohen, B. Lonnerdal, and O. Hernell. 2005. Iron supplements reduce erythrocyte copper-zinc superoxide dismutase activity in term, breastfed infants. *Acta Paediatrica* 94 (11): 1578–1582.

De Benoist, B., E. McLean, I. Egli, and M. Cogswell, ed. 2008. *Worldwide prevalence of anaemia 1993-2005*. Geneva, Switzerland: World Health Organization.

Desai, M. R., J. V. Mei, S. K. Kariuki, K. A. Wannemuehle, P. A. Phillips-Howard, B. L. Nahlen, P. A. Kager, J. M. Vulule, and F. O. ter Kuile. 2003. Randomized controlled trial of daily iron supplementation and `intermittent sulfadoxinepyrimethamine for the treatment of mild childhood anemia in Western Kenya. *Journal of Infectious Diseases* 187: 658–666.

Dewey, K. Increasing iron intake of children through complementary food. 2007. *Food and Nutrition Bulletin* 28 (4 Suppl): S595–609.

Fannati, F., R. Cardin, N. De Maria, G. Della Libera, C. Marafin, E. Lecis, P. Burra, A. Floreani, A. Cecchetto, and R. Naccarato. 1995. Iron storage, lipid peroxidation and glutathione turnover in chronic anti-HCV positive hepatitis. *Journal of Hepatology* 22 (4): 449–456.

Friedman, J. F., J. D. Kurtis, E. R. Kabyemela, M. Fried, and P. E. Duffy. 2009. The iron trap: iron, malaria and anemia at the mother–child interface. *Microbes and Infection* 11 (4): 460–466.

Geram T., and H. P. S. Sachdev. 2002. Effect of iron supplementation on incidence of infectious illness in children: systematic review. *BMJ* 325: 1142–1151.

Grantham-McGregor, S. M., and C. C. Ani. 2001. Undernutrition and mental development. In *Nestlé Nutrition Workshop Series: Clinical Performance Programme, vol. 5*, ed. J.D. Fernstrom, R. Uauy, and P. Arroyo. Basel, Switzerland: Nestec Ltd.

Iannotti, L. M., J. M. Tielsch, J. M. Black, and R. E. Black. 2006 Iron supplementation in early childhood: health benefits and risks. *American Journal of Clinical Nutrition* 84 (6): 1261–1276.

Idjradinata, P., W. E. Watkins, and E. Pollit. 1994. Adverse effect of iron supplementation on weight gain of iron-replete young children. *Lancet* 343: 1252–1254.

International Nutritional Anemia Consultative Group. 2000. *Consensus statement: Safety of iron supplementation programs in malaria endemic regions*. Washington: International life Sciences Institute Press.

Lozoff, B. 2007. Iron deficiency and child development. *Food and Nutrition Bulletin* 28(4): S560–571.

Mebrahtu, T., R. J. Stoltzfus, H. M. Chwaya, J. K. Jape, L. Savioli, A. Montresor, M. Albonico, and J. M. Tiselsch. 2004. Low-dose daily iron supplementation for 12 months does not increase the prevalence of malarial infection or density of parasites in young Zanzibari children. *Journal of Nutrition* 134: 3037–3041.

Menendez, C., J. Todd, P. L. Alonso, N. Francis, S. Lulat, S. Ceesay, B. M'Boge, and B. M. Greenwood. 1994. The effects of iron supplementation during pregnancy, given by traditional birth attendants, on the prevalence of anemia and malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 88: 590–593.

Nacher, M, R. McGready, K. Stepniewska, T. Cho, S. Looareesuwan, N. J. White, and F. Nosten. 2003. Haematinic treatment of anemia increases the risk of Plasmodium vivax malaria in pregnancy *Transactions of the Royal Society of Tropical Medicine and Hygiene* 97: 273–276.

Oppenheimer, S. J. 2001. Iron and its relation to immunity and infectious disease. *Journal of Nutrition* 131: 616S–635S.

Oppenheimer, S. J., S. B. Macfarlane, J. B. Moody, and C. Harrison. 1986. Total dose iron infusion, malaria and pregnancy in Papua New Guinea. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 80: 818–822.

Prentice, A. M. 2008. Iron Metabolism, Malaria, and Other Infections: What Is All the Fuss About? *Journal of Nutrition* 138 (12): 2537–2541.

Prentice, A. M., H. Ghattas, C. Doherty, and S. E. Cox. 2007. Iron metabolism and malaria. *Food and Nutrition Bulletin* 28(4): S524–39.

Rigamonti, C., S. Andorno, E. Maduli, S. Morelli, S. Pittau, G. Nicosia, R. Boldorini, and M. Sartori. 2002. Iron, hepatic stellate cells and fibrosis in chronic hepatitis C. *European Journal of Clinical Investigation* 32 (supplement 1): 28–35.

Romeo, A. M., L. Christen, E. G. Niles, and D. J. Kosman. 2001. Intracellular chelation of iron by bipyridyl inhibits DNA virus replication: ribonucleotide reductase maturation as a probe of intracellular iron pools. *Journal of Biological Chemistry* 276: 24301–24308.

Sazawal, S., R. E. Black, M. Ramsan, H. M. Chwaya, R. J. Stoltzfus, A. Dutta, U. Dhingra, I. Kabole, S. Deb, M. K. Othman, and F. M. Kabole. 2006. 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, randomized, placebo-controlled trial. *Lancet* 367**:** 133–143.

Snow, R. W., J. A. Omumbo, B. Lowe, C. S. Molyneux, J. O. Obiero, A. Palmer, M. W. Weber, M. Pinder, B. Nahlen, C. Obonyo, C. Newbold, S. Gupta, and K. Marsh. 1997. Relation between severe malaria morbidity in children and level of Plasmodium falciparum transmission in Africa. *Lancet* 349: 1650–1654.

Stoltzfus, R. J., and M. Dreyfuss. 1998. *Guidelines for the use of iron supplements to prevent and treat iron deficiency anemia*. Washington, D.C.: ILSI Press.

Stoltzfus, R. J., R. Heidkamp, D. Kenkel, and J. P. Habicht. 2007. Iron supplementation of young children: learning from the new evidence. *Food and Nutrition Bulletin* 28 (4): S572–584.

Tielsch, J. M., S. K. Khatry, R. J. Stoltzfus, J. Katz, S. C LeClerq, R. Adhikari, L. C. Mullany, S. Shresta, and R. E. Black. 2006. Effect of routine prophylactic supplementation with iron and folic acid on preschool child mortality in southern Nepal: community-based, cluster-randomized, placebo-controlled trial. *Lancet* 367: 144–152.

Verhoef, H., C. E. West, and S. M. Nzyuko, S. de Vogel, R. van der Valk, M. A. Wanga, A. Kuijsten, J. Veenemans, and F. J. Kok. 2002. Intermittent administration of iron and sulfadoxine-pyrimethamine to control anaemia in Kenyan children: a randomized controlled trial. *Lancet* 360: 908–914.

Vives Corrons, J. L., A. Miguel-Garcia, M. A. Pujades, A. Miguel-Sosa, S. Cambiazzo, M. Linares, M. T. Dibarrart, and M. A. Calvo. 1995. Increased susceptibility of microcytic red blood cells to in vitro oxidative stress. *European Journal of Hematology* 55 (5): 327–331.

Wang, P., R. K. B. Brobey, T. Horii, P. F. G. Sims, and J. E. Hyde. 1999. Utilization of exogenous folate in the human malaria parasite plasmodium falciparum and its critical role in antifolate drug synergy. *Molecular Microbiology* 32 (6): 1254–1262.

Weinberg, E. D. 1999. The role of iron in protozoan and fungal infectious diseases. *Journal of Eukaryotic Microbiology* 46 (3): 231–238.

World Health Organization. 2007. Conclusions and recommendation of the WHO Consultation on prevention and control of iron deficiency in infants and young children in malaria endemic areas. *Food and Nutrition Bulletin* 28 (4): S621–627.

_____. 2004. Report of the meeting to review results of the zinc/iron supplementation trials conducted in Nepal and Tanzania - Zanzibar, Tanzania, 30 April - 1 May 2004.