Control of iron deficiency anemia in low- and middle-income countries

Sant-Rayn Pasricha,[1-3] Hal Drakesmith,[3] James Black,[1] David Hipgrave,[2] and Beverley-Ann Biggs[2,4]

[1]Nossal Institute for Global Health, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Carlton, Australia; [2]Department of Medicine, Royal Melbourne Hospital, The University of Melbourne, Parkville, Australia; [3]Molecular Immunology and MRC Human Immunology Unit, MRC Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, United Kingdom; and [4]Victorian Infectious Diseases Service, Royal Melbourne Hospital, Parkville, Victoria, Australia

Despite worldwide economic and scientific development, more than a quarter of the world's population remains anemic, and about half of this burden is a result of iron deficiency anemia (IDA). IDA is most prevalent among preschool children and women. Among women, iron supplementation improves physical and cognitive performance, work productivity, and well-being, and iron during pregnancy improves maternal, neonatal, infant, and even long-term child outcomes. Among children, iron may improve cognitive, psychomotor, and physical development, but the evidence for this is more limited. Strategies to control IDA include daily and intermittent iron supplementation, home fortification with micronutrient powders, fortification of staple foods and condiments, and activities to improve food security and dietary diversity. The safety of routine iron supplementation in settings where infectious diseases, particularly malaria, are endemic remains uncertain. The World Health Organization is revising global guidelines for controlling IDA. Implementation of anemia control programs in developing countries requires careful baseline epidemiologic evaluation, selection of appropriate interventions that suit the population, and ongoing monitoring to ensure safety and effectiveness. This review provides an overview and an approach for the implementation of public health interventions for controlling IDA in low- and middle-income countries, with an emphasis on current evidence-based recommendations. (*Blood*. 2013; 121(14):2607-2617)

Introduction

More than 1.6 billion people, almost a quarter of the world's population, are anemic. Despite considerable economic and scientific advancement during recent decades, there has been, at best, only marginal reduction in the global prevalence of anemia.[1] The World Health Organization (WHO) estimates that worldwide, 42% of pregnant women, 30% of nonpregnant women (aged 15 to 50 years), 47% of preschool children (aged 0 to 5 years), and 12.7% of men older than 15 years are anemic (supplemental Figure 1A-C).[1]

Iron deficiency accounts for about half the world's anemia burden.[2] WHO estimates that in 2004, iron deficiency anemia (IDA) resulted in 273 000 deaths: 45% in Southeast Asia, 31% in Africa, 9% in the Eastern Mediterranean, 7% in the Americas, 4% in the Western Pacific, and 3% in Europe, with 97% occurring in low- and middle-income countries. It also caused the loss of 19.7 million disability-adjusted life years, accounting for 1.3% of the global total. Of these lost disability-adjusted life years, 40% were in Southeast Asia, 25% in Africa, and 17% in the Western Pacific; 97% were lost in low- and middle-income countries.[3] The median annual economic loss because of IDA in 10 developing countries was estimated at $16.78 per capita (in 1994 US dollars), or 4% of gross domestic product.[4]

Physicians will be familiar with the clinical diagnosis and management of IDA, but a population approach is required when the prevalence of anemia is high. Hematologists and other physicians may be asked to collaborate with and advise public health and nutrition colleagues in the development of local, district, or national anemia control policies. This review synthesizes the rationale, evidence, experience, and international guidelines concerning population-level approaches for control of IDA to assist hematologists, physicians, nutritionists, and other experts in contributing to public health policy.

Causes of IDA

Iron deficiency may result from inadequate iron intake and absorption, increased iron requirements during growth, and excessive iron losses. Women of reproductive age (WRA) are at particular risk because of menstruation, whereas pregnancy and childbirth result in a net iron loss of 580 to 680 mg because of fetal and placental requirements and bleeding during delivery.[5] In young children, rapid expansion in red cell mass results in very high dietary iron requirements; the US estimated average requirement for iron for a 6- to 12-month-old infant (6.9 mg) exceeds that of an adult male (6 mg).[6] Antenatal and perinatal factors may also influence infant iron status: maternal iron status may influence iron accumulation by the fetus, and maternal hemoglobin and receipt of iron supplementation influence infant iron stores. In addition, maternal iron stores can influence birth weight and duration of gestation: low-birth-weight or premature infants are born with lower iron stores and, thus, are at increased risk for IDA.[7] For these reasons, pregnant and nonpregnant WRA and preschool children are at particular risk for IDA.

A public health approach to resolving the determinants of IDA considers immediate, intermediate, underlying, and fundamental levels

Submitted September 19, 2012; accepted January 18, 2013. Prepublished online as *Blood* First Edition paper, January 25, 2013; DOI 10.1182/blood-2012-09-453522.

The online version of this article contains a data supplement.

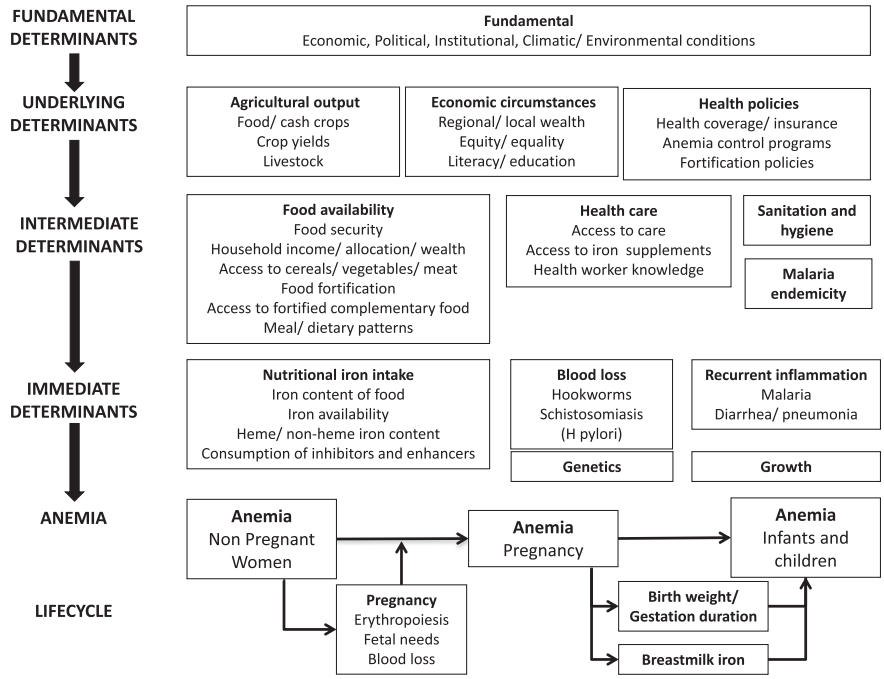

Figure 1. Determinants of iron deficiency anemia. In the public health context, IDA can be considered to have immediate and upstream determinants. Immediate determinants: Intestinal iron absorption is influenced by food factors (type of iron [heme or nonheme] and coconsumption of inhibitors or enhancers of absorption) and host factors (iron stores and genotype for hemoglobinopathy/iron regulation [eg, *TMPRSS6*]). Inhibitors of nonheme iron absorption include phytates, polyphenols (tannins), zinc, and calcium. Hookworms cause chronic gastrointestinal blood loss, and some schistosomes produce intestinal and genitourinary bleeding. *Helicobacter pylori* causes peptic ulcers and may cause resistance to iron therapy. In a term baby, total hemoglobin mass must almost double during the first year; more in ex-preterm or low-birth-weight babies. Iron requirements escalate rapidly during adolescence because of an expansion in hemoglobin and muscle mass and, in girls, menarche. Iron absorption and incorporation into erythrocytes is impaired during malaria (and possibly other) infection and restored after treatment, predominantly mediated by hepcidin. In pregnancy, overall iron requirements exceed 1 g, and each pregnancy results in a net iron loss of 580 to 680 mg. Upstream determinants: Low dietary iron content, consumption of predominantly nonheme iron, and coconsumption of iron with inhibitors of absorption (cereals, grains) result in inadequate iron intake. People in low-income (especially rural) settings may not be able to access fortified foods. Poor sanitation and disposal of human waste promotes bacterial and parasitic (including hookworm) infection, and schistosomiasis follows exposure to freshwater containing infectious larvae. All these factors may be influenced by access to health care, anemia control policies, sanitation practices, agricultural practices, and ultimately, prevailing economic, political, and environmental conditions. (Based on model presented in: "Strategy for Improved Nutrition of Children and Women in Developing Countries", a UNICEF Policy Review, UNICEF, New York, 1990, 36 pp)

of causation (Figure 1). These factors may also apply to minorities or marginalized groups with similarly high rates of IDA in wealthier countries[8] (including indigenous peoples,[9] Hispanics in the United States,[10] and newly arrived refugees[11]).

Effects of alleviation of IDA

Beyond alleviation of symptomatic anemia, the rationale for control of IDA involves putative benefits in important outcomes including childhood cognitive development and growth; cognitive, physical, and psychological health in nonpregnant women; and maternal and neonatal outcomes in pregnant women. Evidence that iron improves these outcomes is critical in estimating the population health effect of controlling iron deficiency.

Effects of iron supplementation in children

Observational studies have identified associations between IDA in infants and cognitive, motor, and behavioral impairment.[12] However, observational findings are susceptible to confounding. This could be overcome by interventional trials, but few randomized controlled trials (RCTs) have compared iron supplementation with control in infants and children. A 2004 systematic review concluded that iron marginally improves older children's mental development but did not benefit children younger than 27 months. The authors suggest that the lack of demonstrable benefit on infants and very young children may reflect the insensitivity of developmental assessment at this age or that harm associated with early iron deficiency may be irreversible.[13] A 2010 meta-analysis found that iron improves psychomotor development at 12 months of age in nonanemic children.[14] Regarding physical growth, a meta-analysis in 2006 found no evidence of significant benefit of iron on any related parameter and found evidence that in developed (but not developing) countries, iron reduces length for age.[15]

Effects of iron supplementation in nonpregnant women

Treatment of women with IDA improves aerobic capacity.[16] Some (but not all) RCTs have shown that iron improves aerobic[17] and endurance capacity,[18] cognitive performance,[19] productivity,[20] symptomatic fatigue,[21] and mood[22] in iron-depleted nonanemic women.

Iron supplementation in pregnancy

A 2009 Cochrane review found that iron supplementation improved birth length and that iron–folic acid (IFA) supplementation improved birth weight.[23] The authors also found evidence that antenatal iron improves Apgar scores and infant ferritin at 3 months and reduces the need for postpartum maternal transfusion, and a large RCT in China recently reported that antenatal iron significantly reduced early neonatal mortality.[24] In addition, an analysis

of long-term outcomes among children of mothers previously enrolled in an RCT in Nepal found that among those whose mothers were randomly assigned to receive antenatal IFA, mortality was reduced by 31% by age 7 years[25] and their inhibitory control, working memory, and fine-motor functioning were better at age 7 to 9 years.[26]

Strategies to address IDA at the population level

Public health interventions to reduce the burden of IDA should address the determinants presented in Figure 1. These may include increasing iron stores through supplementation, fortification of processed or staple food, home food fortification, and increased consumption of food with high iron content and bioavailability. In addition, optimizing maternal nutrition before and during pregnancy, prevention of low birth weight and prematurity, control of parasites, and improvements in access to health care, infant feeding, food security, and socioeconomic status are important factors. WHO has recently revised global guidelines for anemia control, summarized in Table 1.

Iron supplementation

Iron supplementation has long been advocated for anemia control. Oral iron is widely available as a single micronutrient supplement in liquid and tablet formulations, as IFA, or in multiple micronutrient preparations. Different iron compounds have varying bioavailability, effect, and cost. Young children may require iron supplements as liquid formulations, which are more expensive and have a limited shelf life. A systematic review of 55 trials administering iron to children orally, parenterally, or in fortified food found that on average, it improves hemoglobin by 0.74 g/dL and reduces anemia prevalence by 37.9% to 62.3% in non-malaria-endemic settings and 5.8% to 31.8% in malaria-endemic settings.[27] Supplementation may be recommended for daily or intermittent consumption.

Intermittent iron supplementation

The efficacy and acceptability of intermittent (in particular, weekly) iron supplementation to prevent iron deficiency has attracted interest. Absorption of iron from supplements administered intermittently appears higher,[28] possibly mediated by differences in iron-induced changes in intestinal iron transport mechanisms.[29] A Cochrane systematic review evaluating intermittent (1, 2, or 3 times/wk on nonconsecutive days) iron supplementation for nonpregnant women found that compared with no intervention, intermittent iron improves hemoglobin by 4.6 g/L and ferritin by 8.3 μg/L and reduces anemia risk by 27%. The review also compared intermittent iron with daily iron and showed that compared with those receiving daily iron, women receiving intermittent iron had a 26% higher risk for anemia, although final mean hemoglobin concentrations were not dissimilar.[30]

Although many authors have suggested that intermittent iron administration may improve adherence, the Cochrane review did not find evidence for this.[30] A Cochrane review has also compared intermittent (1 to 3 times/wk) with daily iron in pregnancy, with no evidence of difference in infant (birth weight, gestation duration) outcomes; mothers receiving intermittent iron experienced fewer adverse effects but had lower hemoglobin concentrations and increased risk for anemia and iron deficiency at term.[31]

In addition, a Cochrane review comparing intermittent (1 to 3 times/wk) to no iron supplementation for children aged 12 years or younger found that intermittent iron reduces the risk for anemia by 49% and the risk for iron deficiency by 76% and improves hemoglobin and ferritin concentrations by 5.2 g/L and 14.2 μg/L, respectively. When intermittent was compared with daily iron supplementation, daily iron reduced the risk for anemia a further 23%, but hemoglobin and ferritin concentrations were similar.[32]

Most programs implementing intermittent iron have selected weekly IFA supplementation; programs for women and adolescents have been successfully implemented in several countries including Vietnam, India, Cambodia, and Egypt, and in most settings they have reduced anemia, particularly where the baseline prevalence was highest (supplemental Table 1). Thus, although it is probably less effective than daily iron, intermittent iron appears to be a useful option for controlling IDA.

Selection of daily or intermittent iron supplementation

Intermittent iron is cheap to implement (weekly IFA supplementation for women cost between US$0.15 and US$0.36/recipient per annum in India[33]). Directly observed, fixed-day (eg, school-based) administration is feasible with weekly supplementation.[33] Combination with folic acid may also optimize folate status before pregnancy. WHO now recommends weekly supplementation to menstruating women and preschool and school-age children in places where anemia prevalence exceeds 20% (Table 1), updating 2001 recommendations for daily iron supplementation.[2]

Daily administration of iron to children and women during pregnancy may be more appropriate than intermittent supplementation where IDA is known to be highly prevalent and screening for anemia unavailable; in these settings, most individuals in effect require treatment (rather than prophylaxis) for iron deficiency and should benefit from the higher doses.

Fortification

Fortification is a useful public health intervention if the food to be fortified is widely consumed in sufficient amounts by at-risk individuals and if the fortificants do not have a toxic or unappealing effect on the food[34] or significantly increase food prices. Targets for iron fortification include staple foods such as wheat and maize flour and rice (normally processed rice with a tiny proportion of added, reconstituted, and extruded grains); condiments such as salt, curry powder, and fish and soy sauces; and candies. A range of iron fortificants is available.

Ferrous sulfate and fumarate have the highest bioavailability and similar iron content. Ferrous sulfate is cheapest and widely used to fortify flour but may cause rancidity with storage; ferrous fumarate may produce fewer effects on food.[34] Insoluble compounds (ferric pyrophosphate and orthophosphate) have less reactivity with food but poorer bioavailability. Elemental iron compounds have been used but have poor bioavailability and affect taste at effective concentrations. Fortification of cereals, salt, and sauces has been successfully achieved using iron EDTA, which contains iron protected by a chelating moiety that can also improve absorption of intrinsic nonheme dietary iron. Finally, encapsulated ferrous salts, in which iron is encapsulated in an oil layer, have minimal reactivity with the food and offer high bioavailability, but they are relatively expensive. Iron absorption from fortified food may be improved by addition of an enhancer such as ascorbic acid and by minimizing phytate concentration.[34]

Table 1. Global guidelines for the prevention of iron deficiency anemia in the public health context published since 2000

Intervention	Target population	Dose	Agency, year	Systematic review
Intermittent (weekly) iron supplementation	All menstruating adolescent girls and women where prevalence of anemia in this group is 20% or higher.	Iron: 60 mg of elemental iron Folic acid: 2800 μg (2.8 mg)	WHO, 2011[68]	Fernandez-Gaxiola and De-Regil 2011[30]
Intermittent (weekly) iron supplementation	Preschool and school-age children where prevalence of anemia in this group is 20% or higher.	Preschool: 25 mg elemental iron School age: 45 mg elemental iron	WHO, 2011[69]	De-Regil et al 2011[32]
Home fortification with multiple micronutrient powders	Children 6 to 23 mo old where the prevalence of anemia in this group is 20% or higher.	Iron: 12.5 mg elemental iron, preferably as ferrous fumarate Vitamin A: 300 μg retinol Zinc: 5 mg elemental zinc, preferably as zinc gluconate	WHO, 2011[48]	De-Regil et al 2011[70]
Home fortification with multiple micronutrient powders (not recommended)	Pregnant women	N/A	WHO, 2011[71]	Suchdev et al 2011[72]
Daily iron supplementation	All low-birth-weight infants Children 6 to 23 mo old where diet does not provide foods fortified with iron or where anemia prevalence is higher than 40% Children 2 to 5 y old, school-age children, women of childbearing age, pregnant women, and lactating women where anemia prevalence is higher than 40%	Low birth weight: elemental iron: 2 mg/kg/d from birth to 23 mo 6 to 23 mo: elemental iron: 2 mg/kg from 6 to 23 mo old 2 to 5 y: elemental iron: 2 mg/kg (maximum dose, 30 mg) for 3 mo School-age children: iron: 30 mg/d + folic acid: 250 μg/d for 3 mo Women of childbearing age: iron: 60 mg/d + folic acid: 400 μg/d for 3 mo Pregnant women: iron: 60 mg/d + folic acid: 400 μg/d for duration of pregnancy Lactating women: iron: 60 mg/d + folic acid: 400 μg/d for 3 mo post partum	WHO/UNU/UNICEF, 2001[2]	N/A
Optimization of food-based approaches to controlling anemia (ie, improvement of dietary diversity, changing meal patterns to ensure optimal iron absorption [minimize inhibitors and increase enhancers of iron absorption])	Community-wide	N/A	WHO/UNU/UNICEF, 2001[2]	N/A
Wheat and maize flour fortification	Consider when industrially produced wheat or maize flour is consumed by a large proportion of the population of the country	Fortification with iron, folic acid, zinc, B12, and vitamin A recommended; formulation and dose based on average per capita wheat flour availability	WHO, FAO, UNICEF, GAIN, MI, FFI, 2009[73]	N/A
Nutrient content of complementary foods in infants: meat, poultry, fish, or eggs should be eaten daily or as often as possible. Vegetarian diets cannot meet nutrient needs at this age unless nutrient supplements or fortified products are used.	Use fortified complementary foods as needed.	Not specified	PAHO[74]	N/A

CDC, Centers for Disease Control and Prevention; FAO, Food and Agriculture Organization of the United Nations; FFI, Flour Fortification Initiative; GAIN, Global Alliance for Improved Nutrition; MI, Micronutrient Initiative; UNICEF, United Nations Children's Fund; WHO, World Health Organization; PAHO: Pan American Health Organization.

Table 1. (continued)

Intervention	Target population	Dose	Agency, year	Systematic review
Periodic deworming for soil-transmitted helminths	Where prevalence among school age children is higher than 50%: twice-yearly deworming for preschool and school-age children, women of reproductive age, and selected others at high risk. Where prevalence among school age children is 20% to 50%: once-yearly deworming for preschool and school-age children, women of reproductive age, and selected others at high risk.	Albendazole (200 mg for children younger than 2 y; otherwise 400 mg) or mebendazole (500 mg)	WHO, 2006[75]	N/A
Periodic deworming for schistosomiasis	High-risk community: When there is higher than 50% infection by microscopy or higher than 30% visible hematuria, there should be annual treatment of all school-age children and selected others; medium-risk community: When there is 10% to 50% infection by microscopy or less than 30% visible hematuria, school-age children and selected others should be treated every 2 y; low-risk community: Where there is less than 10% infection by microscopy, school-age children should be treated twice during the school year.	Praziquantel (dose dependent on height)	WHO, 2006[75]	N/A
Monitoring and Evaluation				
The measurement of the iron status of populations is best achieved using serum ferritin and soluble transferrin receptor; measurement of hemoglobin should also be undertaken, and measurement of an indicator of inflammation (eg, C-reactive protein, α-1 glycoprotein) should be undertaken where infection/inflammation is common.			WHO/CDC, 2007[58]	WHO/CDC[58]
Serum ferritin is the best indicator of a response to an intervention to control iron deficiency and should be measured with the hemoglobin concentration in program evaluations. If funding is available, it could also be useful to measure the concentration of an acute-phase protein (ie, C-reactive protein, α-1 glycoprotein).				
Logic model for program theory for implementation of micronutrient supplementation in various settings			WHO/CDC, 2011[76]	N/A
Other Approaches				
Delayed clamping of the umbilical cord at 30 to 120 s after delivery			WHO, 2009[41]	McDonald 2008[77]

CDC, Centers for Disease Control and Prevention; FAO, Food and Agriculture Organization of the United Nations; FFI, Flour Fortification Initiative; GAIN, Global Alliance for Improved Nutrition; MI, Micronutrient Initiative; UNICEF, United Nations Children's Fund; WHO, World Health Organization; PAHO: Pan American Health Organization.

Fortification may be performed centrally at the point of food manufacture or closer to the consumer, and fortification of staple foods can be made mandatory by regulators. However, quality control can be difficult in large countries with thousands of food producers. Another limitation of centralized fortification is that the people with the greatest need, such as subsistence farmers, may consume the smallest amounts of fortified food. In such cases, local fortification of locally produced foods may be preferable if quality control can be assured. WHO recommends wheat and maize flour fortification where feasible (Table 1).

Multiple micronutrient powders

Infants and young children depend on complementary foods to provide the majority of their iron requirement after the first 6 months. However, iron-rich complementary foods are often inaccessible for families in low-income settings. For example, in rural India, the daily iron intake from complementary foods among children aged 12 to 23 months was only 11.7% of that recommended.[35] WHO suggests that infants who do not receive adequate meat, fish, or eggs receive iron-fortified complementary foods (Table 1), and the American Academy of Pediatrics recommends that iron-fortified cereals or meat be introduced after about 6 months of exclusive breast-feeding.[36,37]

An important emerging strategy in the control of micronutrient deficiency is the introduction of home-based fortification with micronutrient powders (MNPs) such as "Sprinkles." In these preparations, iron is encapsulated in a lipid layer that prevents adverse effects on food flavor and appearance. The preparations are supplied as single-dose sachets and added to the child's meal once it has been served ("home fortification"). Clinical trials have demonstrated that MNPs have efficacy comparable to liquid ferrous sulfate in controlling anemia[38] and have improved iron and micronutrient status among children in Asia and Africa and in indigenous communities of developed countries.[39] A recent Cochrane review evaluated the use of home fortification with MNPs among children younger than 2 years: Compared with placebo, MNPs reduced anemia by 31% and iron deficiency by 51%, but data were insufficient to compare the efficacy of MNPs with that of iron supplements. Important limitations of this approach include the higher cost of MNPs compared with iron supplements (but perhaps not with liquid formulations), large quantities of waste associated with packaging, and limited availability (although manufacture is being scaled up). WHO guidelines support home fortification with MNPs for children aged 6 to 23 months where the anemia prevalence in this group exceeds 20% (Table 1).

Antihelminthic therapy

Deworming increases hemoglobin concentrations and reduces the prevalence of anemia.[40] Periodic, community-wide administration of albendazole or mebendazole for soil-transmitted helminths and praziquantel for schistosomiasis is recommended for communities with high infection burdens (Table 1).

Other approaches

Delayed umbilical cord clamping allows the additional transfer of ~100 mL of placental blood to the infant. WHO recommends delayed cord clamping but mentions the risk for polycythemia and neonatal jaundice (Table 1).[41] However, a recent RCT found that clamping before administration of oxytocin, 3 minutes postdelivery, improved infant iron stores at 4 months with no increased need for phototherapy.[42]

Dietary nonheme iron bioavailability can be increased by minimizing intake of absorption inhibitors (eg, phytates and polyphenols) and increasing intake of enhancers (eg, ascorbate) through optimized food preparation and meal patterns.[2] Biofortification through conventional (selective) and transgenic breeding to enhance the micronutrient (including iron) content of foods such as rice, beans, sweet potato, and banana is emerging as a potentially effective strategy.[43] The ultimate goal is to prevent undernutrition by enabling an optimal intake of nutrient-rich foods through reduction in food insecurity and poverty alleviation (Figure 1).

Risks of routine iron supplementation

Interactions with malaria

There are concerns about the potential adverse effects of population-based iron supplementation for children in malaria-endemic areas. In 2006, a large RCT comparing IFA with placebo in children aged 1 to 35 months in Tanzania (where malaria transmission is intense) found significant increases in death, serious adverse events, hospital admissions, and serious events caused by malaria among children receiving IFA. A substudy suggested that this harm was not seen among children with baseline IDA.[44] A subsequent Cochrane review evaluating 68 trials of iron supplementation in malaria-endemic areas found that iron supplementation did not increase the overall risk for clinical malaria or death, but the risk for clinical malaria among children receiving iron was higher in studies that did not undertake active surveillance for malaria. In addition, malarial parasitemia was higher among participants receiving iron.[45] A longitudinal study in Tanzania found that iron deficiency protected young children from malaria.[46] Erythrocyte incorporation of orally administered iron is suppressed in children with postmalarial anemia mediated by hepcidin.[47]

The balance of benefit and harm may depend on the intensity of malaria transmission and local immunity to malaria, the prevalence of iron deficiency, and the general health of the population. Ideally, iron should only be dispensed to children who will absorb it and use it for erythropoiesis and in whom it will be safe. WHO advises that among children "in malaria-endemic areas, the provision of iron should be implemented in conjunction with measures to prevent, diagnose and treat malaria".[48] In addition, we suggest that children with fever or suspected clinical malaria should not consume iron supplements, including MNPs containing iron, until they have recovered. In holoendemic settings, if malaria control is weak, clinical case detection and treatment of anemic children should be performed. Formal measurement of iron status to confirm deficiency should precede supplementation if possible, but this is usually unavailable in such locations.

Iron overload

The safety of iron intervention programs for populations in which conditions causing nonphysiologic enhanced iron absorption (such as hereditary hemochromatosis; possibly heterozygote, homozygote, and compound heterozygote thalassemia conditions;[49] and chronic hemolytic anemia) are prevalent is not well understood. Epidemiologic data for thalassemia intermedia, E-β thalassemia, and hemoglobin H disease[50] are incomplete,[51] especially in low- and middle-income settings; may underestimate the true burden; and exhibit heterogeneity between different communities.[51] These conditions may be mild or asymptomatic and not reach clinical diagnosis and are common in

Asian populations where anemia is prevalent. Affected individuals may be at risk for iron overload. Pyruvate kinase deficiency is a relatively common nonspherocytic hemolytic anemia, affecting between less than 0.1% and 3.4% of Chinese populations.[52] Individuals with this condition are at risk for iron overload resulting from erythroid suppression of hepcidin.[53]

The safety of long-term iron supplementation in hemoglobinopathy carriers (5.2% of the world's population)[54] has not been clearly established. In one study, supplementation to pregnant women with hemoglobulin E heterozygote or homozygote states did not seem to cause iron overload.[55]

Hemoglobinopathies contribute considerably but variably to the burden of anemia, potentially distorting estimates of the prevalence of IDA.[54] For example, in Thailand, hemoglobinopathy was found to be a greater contributor to anemia than iron deficiency in schoolchildren and pregnant women,[56,57] whereas in rural Indian children, hemoglobinopathy was only a minor contributor.[35]

WHO does not offer guidance on iron supplementation or fortification in settings where hemoglobinopathies and other inherited red cell disorders are prevalent. We suggest that where such disorders are likely to be prevalent, a baseline epidemiologic evaluation of both hemoglobin and iron indices should be undertaken to establish the relative contributions of iron deficiency and non-iron deficiency to the overall burden of anemia. Ideally, specific evaluation for thalassemia should also be performed. Iron supplementation programs should then target pregnant and nonpregnant WRA and children, who are at lowest risk for iron overload. Their safety can then be monitored through follow-up surveys to measure changes in anemia prevalence and, ideally, assessment for iron overload. Publication of these data is essential for developing the literature on this subject.

Other risks

Other risks with iron supplementation include gastrointestinal adverse effects that limit adherence and, in children, a risk for toxicity in overdose. Another risk is the possibility that in iron-replete children, iron may actually impair growth.[15]

Implementation of anemia control programs

Population-level anemia control strategies should be sustainable, given available resources; should involve input from relevant government and nongovernment health and nonhealth (eg, education, agriculture) agencies[2]; should involve consultation and partnerships with targeted communities and the food industry; and should incorporate monitoring and evaluation to ensure efficacy and safety. The strategies also should include adequate community and food industry education and marketing to optimize the uptake of interventions, perhaps through public–private partnerships. In addition, solutions should be tailored to the local context. For example, natural disasters and complex emergencies may exacerbate the burden of iron deficiency and require a combination of short-term supplementation, fortified rations, and treatment of infections.

Figure 2 suggests an approach to the implementation of strategies to control IDA. Baseline and follow-up evaluation of anemia prevalence are critical to effective planning and monitoring.

Estimation of the prevalence of anemia

Hemoglobin and ferritin are considered by WHO to be the most effective indices for determining the population burden of IDA (Table 1).[58] A variety of methods for measuring hemoglobin are available in the laboratory, at point-of-care, and in the field. Although the cyanmethemoglobin method is routinely used in automated instruments, in many low-income settings, photoelectric calorimeters can perform manual cyanmethemoglobin-based measurements; however, this requires careful dilution of patient samples, regular calibration, and electricity.[59] The HemoCue AB (Angelholm, Sweden) portable hemoglobinometer provides a point-of-care measure of hemoglobin from a capillary or venous sample, includes in-built quality control, and uses proprietary cuvettes to facilitate calibration. It uses a rechargeable battery and has been widely used in many field studies, but it is also relatively expensive.

Other methods of hemoglobin estimation are probably too inaccurate for population studies. These include filter paper methods and the WHO Hemoglobin Color Scale, the copper sulfate method, the Sahli method, microhematocrit estimation, and clinical examination. Portable devices for noninvasive hemoglobin estimation by cooximetry have been developed and may be useful in the field once improvement in bias and limits of agreement have been achieved.[60]

WHO and the Centers for Disease Control and Prevention hemoglobin cutoffs that define anemia are summarized in supplemental Table 2. Neither WHO nor the Centers for Disease Control and Prevention distinguish hemoglobin cutoffs based on race. However, data from the third US National Health and Nutrition Examination Survey and a cohort of patients in San Diego, California, found that the normal ranges do vary by race,[61] possibly because of ethnic differences in carriage of hemoglobinopathies and conceivably influenced by polymorphisms in genes related to regulation of iron balance (eg, *TMPRSS6*).[62] In young children, definitions of anemia are especially difficult, as hemoglobin concentrations change rapidly, and the suggested ranges may be too high.[63]

Estimation of the prevalence of iron deficiency

IDA is defined when anemia and iron deficiency coexist. To establish the prevalence of IDA, determination of the prevalence of iron deficiency itself should be undertaken where feasible. However, measurement of iron indices generally requires an adequate sample of blood, serum separation, and automated analysis of specimens; thus, specimens need to be centrifuged, frozen, and transported to equipped laboratories. The resources or electricity to overcome these barriers can be difficult in poor rural areas.

Although serum ferritin is considered the most useful iron index in the public health context by WHO, it is an acute-phase reactant and may underestimate the prevalence of iron deficiency where there is a high burden of clinical or subclinical infection/inflammation. Strategies to overcome this limitation include the measurement of another inflammatory marker (eg, α-1 glycoprotein or C-reactive protein) with adjustment of the ferritin level or cutoff for iron deficiency as appropriate.[2,64]

The WHO threshold for diagnosis of iron deficiency in adults is ferritin levels lower than 15 ng/mL, and levels lower than 12 ng/mL for children younger than 5 years (<30 ng/mL where inflammation is coexistent).[2] Alternatively, or in addition, the soluble transferrin receptor (sTfR) is stable in inflammation, and its measurement also enables calculation of the sTfR–ferritin index, a useful indicator of iron stores where inflammation and infection are prevalent. Cutoffs of sTfR (and, thus, the sTfR–ferritin index) depend on the assay used,

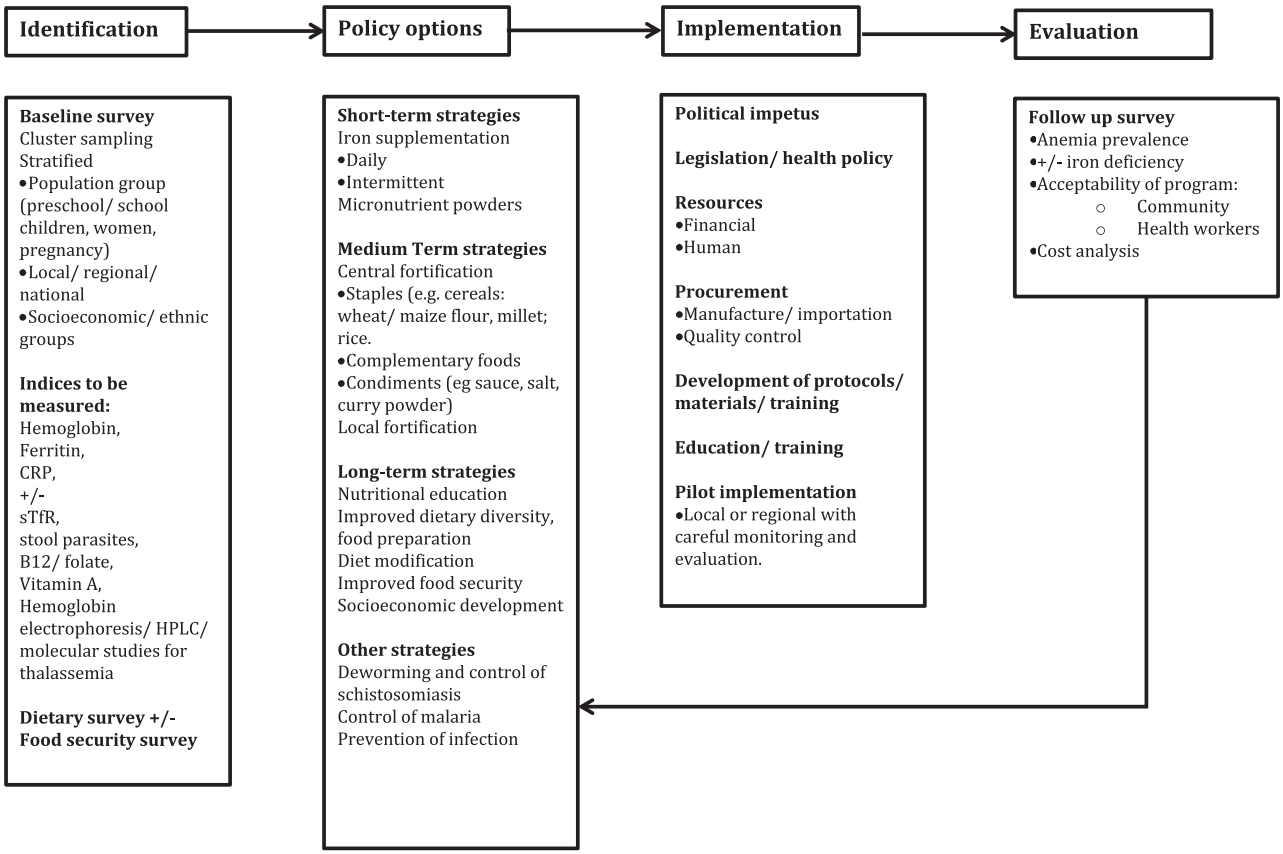

Figure 2. Implementation of anemia control programs. Project cycle for anemia control program. Following evaluation of the baseline epidemiology of anemia, a combination of short, medium and longer-term solutions can be selected. Anemia control may be integrated with existing functioning health programs; for example: antenatal care, infant and young child programs (eg, Integrated Management of Neonatal and Childhood Illnesses, immunization programs, vitamin A supplementation, school health checks, reproductive health education, family planning, premarital or other screening). Complementary strategies such as deworming and control of schistosomiasis may be beneficial. Where malaria is endemic, malaria control interventions should be in place. Monitoring and evaluation should enable improvements in the design and ongoing implementation of the program.

which is a key limitation of these indices. Zinc protoporphyrin is a useful index of moderate and severe IDA, can be measured using a portable hematofluorometer, and has also been used extensively in field studies, but it may also be affected by anemia of chronic disease and hemoglobinopathy. Reticulocyte hemoglobin concentration provides an index of iron status if capable automated hematology analyzers are accessible from the field site.[58] Serum or urine hepcidin may emerge as a useful index of iron stores and predictor of iron absorption, especially if point-of-care assays can be developed.[47]

Design of epidemiologic studies

Cross-sectional surveys are the most appropriate way to determine the population prevalence of anemia. Both preschool and school-aged children and nonpregnant and pregnant WRA should be included. The survey design is informed by whether the estimates of anemia prevalence should represent nation, region, or some other area and whether estimates for any particular group (ethnic, socioeconomic, etc) need to be especially precise, incorporating stratified sampling.

Community (eg, household) sampling is preferable to clinic-based sampling unless most members of the population attend (eg, antenatal clinics). School-based sampling is useful for studying schoolchildren. Cluster-based sampling is commonly used and involves random selection of villages or schools, with probability of selection according to population size. Individuals within each cluster are then randomly or systematically sampled, which limits the number of locations to which investigators must travel to complete the survey. However, surveys using cluster sampling require a larger sample size to account for intracluster similarities (the so-called design effect). Experience suggests that for anemia studies, the sample size should be multiplied two- to threefold. Sampling 30 individuals each from 30 clusters generally provides adequately precise estimates of anemia prevalence.[65] A detailed discussion of study designs for estimating anemia prevalence is available.[66]

Future research priorities

Basic, clinical, epidemiologic, and operational research is required to optimize anemia reduction strategies in developing countries.

Evidence to develop guidelines for iron supplementation programs in areas of high infection pressure (especially malaria) is inadequate. Laboratory and field studies may provide an improved mechanistic and clinical understanding of this interaction. An improved understanding of the interplay between infection, inflammation, erythropoietic requirements, and hypoxia, orchestrated by hepcidin, may help identify how to design and target iron interventions that will provide the greatest benefit and least risk. Rather than population-wide coverage of iron interventions, directed interventions after point-of-care screening of iron status (eg, of hepcidin)

and infection might be a useful future strategy. Simpler strategies such as deferring iron supplementation to febrile children until convalescence or until after the malaria season should also be evaluated.

Deficiencies of other micronutrients (particularly folate and vitamins B12 and A), infections such as malaria, anemia of chronic disease, and genetic disorders of hemoglobin and red cell enzymes may substantially contribute to the burden of anemia in developing settings.[57] There is an urgent need to clarify the relative contribution of these conditions to the overall burden of anemia in different geographic and demographic settings. The safety, particularly with regard to iron overload, of supplementation and fortification in populations in which hemoglobinopathy and other inherited red cell disorders are prevalent requires urgent clarification.

The cutoffs for hemoglobin that define anemia remain uncertain, especially in children and where hemoglobinopathies are common. Optimal statistical and functional cutoffs for anemia should be defined in diverse populations.

Despite the many studies in this area, the clinical benefits and risks of iron supplementation (and other modes of delivery) need further exploration and study in well-designed, adequately powered RCTs. It is no longer necessary to undertake studies reporting iron status, hemoglobin, or anemia as primary endpoints; instead, functional outcomes (ie, in children: cognitive and physical development, growth, and morbidity from infectious diseases; in women: cognitive, psychological, and physical well-being and economic productivity; in pregnancy: maternal and fetal and infant outcomes) should be measured.[67]

Conclusion

Supplementation with iron and provision of iron and other micronutrients through home fortification with MNPs can be relatively quickly implemented and are likely to rapidly improve iron stores but are medical short-term solutions. Medium-term strategies, such as food fortification and biofortification, may take some years to plan, pilot, and implement. Long-term solutions involve genuine changes in food security and diet and may require fundamental socioeconomic and dietary change as well as commercial approaches but are, of course, an ultimate aim of development. A comprehensive approach to anemia control would simultaneously encompass short-, medium-, and long-term interventions together with companion strategies (Figure 2). Once medium- and long-term interventions are established, short-term solutions could be withdrawn. Iron interventions will only benefit iron-deficient individuals, and thus should be targeted at populations in which iron deficiency makes a major contribution to anemia.

Where no control policy is in place and anemia is prevalent, the priority should be ensuring iron (together with folate) is provided from early pregnancy, as this can improve both maternal and infant outcomes and is safe, cheap, and simple to implement. Providing iron to nonpregnant WRA, older infants, and young children can then follow, together with medium- and longer-term strategies.

Although distribution of iron has been recommended by international organizations for many years, there has been minimal improvement in the burden of anemia in many low-income settings. Optimized public health systems and partnerships between funders, policymakers, and program managers are needed to develop and implement anemia control interventions and to ensure their safe and effective delivery by health workers in the field to the people who are at risk.

Acknowledgments

The authors thank WHO for permission to use images depicted in supplemental Figure 1.

Authorship

Contribution: S.-R.P., H.D., J.B., D.H., and B-A.B. wrote the paper.

Conflict-of-interest disclosure: S.-R.P. has served as an intern with the Micronutrients Unit at Department of Nutrition for Health and Development at WHO; was rapporteur for the Nutrition Guidance Expert Advisory Group meeting in March 2011, which reviewed new global guidelines for anemia control; has received an unrestricted research grant as a coinvestigator from Vifor Pharma Ltd; and has served as a consultant to the Meat & Livestock Authority Australia. B.-A.B. has served as a member of the World Health Organization Nutrition Guidance Expert Advisory Group in 2010-2011 and was involved in development of new global guidelines for anemia control. The remaining authors declare no competing financial interests.

Correspondence: Sant-Rayn Pasricha, Nossal Institute for Global Health, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Carlton, Victoria 3010 Australia; e-mail: sant-rayn.pasricha@unimelb.edu.au.

References

1. Benoist B, McLean E, Egli I, et al. *Worldwide Prevalence of Anaemia 1993-2005.* Geneva, Switzerland: World Health Organization; 2008.
2. World Health Organization /UNICEF/UNU. *Iron Deficiency Anaemia: Assessment, Prevention, and Control. A Guide for Programme Managers.* Geneva, Switzerland: World Health Organization; 2001.
3. Mathers C, Steven G, Mascarenhas M. *Global Health Risks: Mortality and Burden of Disease Attributable to Selected Major Risks.* Geneva, Switzerland: World Health Organization; 2009.
4. Horton S, Ross J. The economics of iron deficiency. *Food Policy.* 2003;28:51-75.
5. Bothwell TH. Iron requirements in pregnancy and strategies to meet them. *Am J Clin Nutr.* 2000; 72(1 suppl):257S-264S.
6. Part III. Vitamins and minerals. In: Otten JJ, Hellwig JP, Meyers LD, eds. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements.* Washington, DC: The National Academies Press; 2006.
7. Chaparro CM. Setting the stage for child health and development: Prevention of iron deficiency in early infancy. *J Nutr.* 2008;138(12):2529-2533.
8. Park K, Kersey M, Geppert J, Story M, Cutts D, Himes JH. Household food insecurity is a risk factor for iron-deficiency anaemia in a multi-ethnic, low-income sample of infants and toddlers. *Public Health Nutr.* 2009;12(11):2120-2128.
9. Khambalia AZ, Aimone AM, Zlotkin SH. Burden of anemia among indigenous populations. *Nutr Rev.* 2011;69(12):693-719.
10. Brotanek JM, Gosz J, Weitzman M, Flores G. Iron deficiency in early childhood in the United States: Risk factors and racial/ethnic disparities. *Pediatrics.* 2007;120(3):568-575.
11. Johnston V, Smith L, Roydhouse H. The health of newly arrived refugees to the Top End of Australia: Results of a clinical audit at the Darwin Refugee Health Service. *Aust J Prim Health.* 2012;18(3):242-247.
12. Grantham-McGregor S, Ani C. A review of studies on the effect of iron deficiency on cognitive development in children. *J Nutr.* 2001;131(2S-2): 649S-666S.

13. Sachdev H, Gera T, Nestel P. Effect of iron supplementation on mental and motor development in children: Systematic review of randomised controlled trials. *Public Health Nutr.* 2005;8(2):117-132.
14. Szajewska H, Ruszczynski M, Chmielewska A. Effects of iron supplementation in nonanemic pregnant women, infants, and young children on the mental performance and psychomotor development of children: A systematic review of randomized controlled trials. *Am J Clin Nutr.* 2010;91(6):1684-1690.
15. Sachdev H, Gera T, Nestel P. Effect of iron supplementation on physical growth in children: Systematic review of randomised controlled trials. *Public Health Nutr.* 2006;9(7):904-920.
16. Radjen S, Radjen G, Zivotic-Vanovic M, Radakovic S, Vasiljevic N, Stojanovic D. [Effect of iron supplementation on maximal oxygen uptake in female athletes]. *Vojnosanit Pregl.* 2011;68(2): 130-135.
17. Brownlie T, Utermohlen V, Hinton PS, Giordano C, Haas JD. Marginal iron deficiency without anemia impairs aerobic adaptation among previously untrained women. *Am J Clin Nutr.* 2002;75(4):734-742.
18. Hinton PS, Giordano C, Brownlie T, et al. Iron supplementation improves endurance after training in iron-depleted, nonanemic women. *J Appl Physiol.* 2000;88(3):1103-1111.
19. Murray-Kolb LE, Beard JL. Iron treatment normalizes cognitive functioning in young women. *Am J Clin Nutr.* 2007;85(3):778-787.
20. Li R, Chen X, Yan H, et al. Functional consequences of iron supplementation in iron-deficient female cotton mill workers in Beijing, China. *Am J Clin Nutr.* 1994;59(4):908-913.
21. Verdon F, Burnand B, Stubi CL, et al. Iron supplementation for unexplained fatigue in non-anaemic women: Double blind randomised placebo controlled trial. *BMJ.* 2003;326(7399): 1124.
22. McClung JP, Karl JP, Cable SJ, et al. Randomized, double-blind, placebo-controlled trial of iron supplementation in female soldiers during military training: Effects on iron status, physical performance, and mood. *Am J Clin Nutr.* 2009;90(1):124-131.
23. Pena-Rosas JP, Viteri FE. Effects of routine oral iron supplementation with or without folic acid for women during pregnancy. *Cochrane Database Syst Rev.* 2006;(3):CD004736.
24. Zeng L, Dibley MJ, Cheng Y, et al. Impact of micronutrient supplementation during pregnancy on birth weight, duration of gestation, and perinatal mortality in rural western China: Double blind cluster randomised controlled trial. *BMJ.* 2008;337:a2001.
25. Christian P, Stewart CP, LeClerq SC, et al. Antenatal and postnatal iron supplementation and childhood mortality in rural Nepal: A prospective follow-up in a randomized, controlled community trial. *Am J Epidemiol.* 2009;170(9):1127-1136.
26. Christian P, Murray-Kolb LE, Khatry SK, et al. Prenatal micronutrient supplementation and intellectual and motor function in early school-aged children in Nepal. *JAMA.* 2010;304(24): 2716-2723.
27. Gera T, Sachdev HP, Nestel P, et al. Effect of iron supplementation on haemoglobin response in children: Systematic review of randomised controlled trials. *J Pediatr Gastroenterol Nutr.* 2007;44(4):468-486.
28. Ruivard M, Feillet-Coudray C, Rambeau M, et al. Effect of daily versus twice weekly long-term iron supplementation on iron absorption and status in iron-deficient women: A stable isotope study. *Clin Biochem.* 2006;39(7):700-707.
29. Frazer DM, Wilkins SJ, Becker EM, et al. A rapid decrease in the expression of DMT1 and Dcytb but not Ireg1 or hephaestin explains the mucosal block phenomenon of iron absorption. *Gut.* 2003; 52(3):340-346.
30. Fernandez-Gaxiola AC, De-Regil LM. Intermittent iron supplementation for reducing anaemia and its associated impairments in menstruating women. *Cochrane Database Syst Rev.* 2011;(12): CD009218.
31. Pena-Rosas JP, De-Regil LM, Dowswell T, Viteri FE. Intermittent oral iron supplementation during pregnancy. *Cochrane Database Syst Rev.* 2012;(7):CD009997.
32. De-Regil LM, Jefferds ME, Sylvetsky AC, Dowswell T. Intermittent iron supplementation for improving nutrition and development in children under 12 years of age. *Cochrane Database Syst Rev.* 2011;(12):CD009085.
33. World Health Organization. *Prevention of Iron Deficiency Anaemia in Adolescents. Role of Weekly Iron and Folic Acid Supplementation.* New Delhi, India: World Health Organization Regional Office for South East Asia; 2011.
34. Allen L, de Benoist B, Dary O, et al. *Guidelines on Food Fortification with Micronutrients.* Geneva, Switzerland: World Health Organization, Food and Agricultural Organization of the United Nations; 2006.
35. Pasricha SR, Black J, Muthayya S, et al. Determinants of anemia among young children in rural India. *Pediatrics.* 2010;126(1):e140-e149.
36. Kleinman RE, ed. Pediatric Nutrition Handbook. Elk Grove Village, Illinois: American Academy of Pediatrics; 2009.
37. Section on Breastfeeding. Breastfeeding and the use of human milk. *Pediatrics.* 2012;129(3):e827–e841.
38. Zlotkin S, Arthur P, Schauer C, et al. Home-fortification with iron and zinc sprinkles or iron sprinkles alone successfully treats anemia in infants and young children. *J Nutr.* 2003;133(4): 1075-1080.
39. Zlotkin SH, Schauer C, Christofides A, Sharieff W, Tondeur MC, Hyder SM. Micronutrient sprinkles to control childhood anaemia. *PLoS Med.* 2005; 2(1):e1.
40. Gulani A, Nagpal J, Osmond C, Sachdev HP. Effect of administration of intestinal anthelmintic drugs on haemoglobin: Systematic review of randomised controlled trials. *BMJ.* 2007; 334(7603):1095.
41. Abalos E. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes: RHL commentary (last revised: March 2, 2009). The World Health Organization Reproductive Health Library. Vol 2012. Geneva, Switzerland: World Health Organization; 2009.
42. Andersson O, Hellstrom-Westas L, Andersson D, Domellof M. Effect of delayed versus early umbilical cord clamping on neonatal outcomes and iron status at 4 months: A randomised controlled trial. *BMJ.* 2011;343:d7157.
43. Nestel P, Bouis HE, Meenakshi JV, et al. Biofortification of staple food crops. *J Nutr.* 2006; 136(4):1064-1067.
44. Sazawal S, Black RE, Ramsan M, 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(9505):133-143.
45. Ojukwu JU, Okebe JU, Yahav D, Paul M. Oral iron supplementation for preventing or treating anaemia among children in malaria-endemic areas. *Cochrane Database Syst Rev.* 2009;(3): CD006589.
46. Gwamaka M, Kurtis JD, Sorensen BE, et al. Iron deficiency protects against severe Plasmodium falciparum malaria and death in young children. *Clin Infect Dis.* 2012;54(8):1137-1144.
47. Prentice AM, Doherty CP, Abrams SA, et al. Hepcidin is the major predictor of erythrocyte iron incorporation in anemic African children. *Blood.* 2012.
48. World Health Organization. Use of multiple micronutrient powders for home fortification of foods consumed by infants and children 6-23 months of age. Geneva, Switzerland: World Health Organization; 2011.
49. Zimmermann MB, Fucharoen S, Winichagoon P, et al. Iron metabolism in heterozygotes for hemoglobin E (HbE), alpha-thalassemia 1, or beta-thalassemia and in compound heterozygotes for HbE/beta-thalassemia. *Am J Clin Nutr.* 2008; 88(4):1026-1031.
50. Lemmens-Zygulska M, Eigel A, Helbig B, et al. Prevalence of alpha-thalassemias in northern Thailand. *Hum Genet.* 1996;98(3):345-347.
51. Weatherall DJ. The inherited diseases of hemoglobin are an emerging global health burden. *Blood.* 2010;115(22):4331-4336.
52. Feng CS, Tsang SS, Mak YT. Prevalence of pyruvate kinase deficiency among the Chinese: Determination by the quantitative assay. *Am J Hematol.* 1993;43(4):271-273.
53. Rider NL, Strauss KA, Brown K, et al. Erythrocyte pyruvate kinase deficiency in an old-order Amish cohort: Longitudinal risk and disease management. *Am J Hematol.* 2011;86(10): 827-834.
54. Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. *Bull World Health Organ.* 2008;86(6): 480-487.
55. Sanchaisuriya K, Fucharoen S, Ratanasiri T, et al. Effect of the maternal betaE-globin gene on hematologic responses to iron supplementation during pregnancy. *Am J Clin Nutr.* 2007;85(2): 474-479.
56. Sukrat B, Sirichotiyakul S. The prevalence and causes of anemia during pregnancy in Maharaj Nakorn Chiang Mai Hospital. *J Med Assoc Thai.* 2006;89(Suppl 4):S142-S146.
57. Thurlow RA, Winichagoon P, Green T, et al. Only a small proportion of anemia in northeast Thai schoolchildren is associated with iron deficiency. *Am J Clin Nutr.* 2005;82(2):380-387.
58. World Health Organization and Centers for Disease Control and Prevention. Assessing the Iron Status of Populations: Including Literature Reviews. Report of a Joint World Health Organization/Centers for Disease Control and Prevention Technical Consultation on the Assessment of Iron Status at the Population Level, Geneva, Switzerland, 6–April 8, 2004. Geneva, Switzerland: World Health Organization/ Centers for Disease Control and Prevention; 2007.
59. PATH. Anemia Detection Methods in Low-Resource Settings: A Manual for Health Workers. Seattle, Washington: USAID; 1997.
60. Gayat E, Aulagnier J, Matthieu E, Boisson M, Fischler M. Non-invasive measurement of hemoglobin: Assessment of two different point-of-care technologies. *PLoS One.* 2012;7(1): e30065.
61. Beutler E, Waalen J. The definition of anemia: What is the lower limit of normal of the blood hemoglobin concentration? *Blood.* 2006;107(5): 1747-1750.
62. Chambers JC, Zhang W, Li Y, et al. Genome-wide association study identifies variants in TMPRSS6 associated with hemoglobin levels. *Nat Genet.* 2009;41(11):1170-1172.

63. Domellöf M, Dewey KG, Lönnerdal B, et al. The diagnostic criteria for iron deficiency in infants should be reevaluated. *J Nutr.* 2002;132(12): 3680-3686.

64. Thurnham DI, McCabe LD, Haldar S, Wieringa FT, Northrop-Clewes CA, McCabe GP. Adjusting plasma ferritin concentrations to remove the effects of subclinical inflammation in the assessment of iron deficiency: A meta-analysis. *Am J Clin Nutrition.* 2010;92(3): 546-555.

65. Binkin N, Sullivan K, Staehling N, Nieburg P. Rapid nutrition surveys: How many clusters are enough? *Disasters.* 1992;16(2): 97-103.

66. Gorstein J, Sullivan KM, Parvanta I, et al. Indicators and Methods for Cross-Sectional Surveys of Vitamin and Mineral Status of Populations. Atlanta, Georgia: The Micronutrient Initiative and the Centers for Disease Control and Prevention; 2007.

67. Stoltzfus RJ. Research needed to strengthen science and programs for the control of iron deficiency and its consequences in young children. *J Nutr.* 2008;138(12):2542-2546.

68. World Health Organization. *Guideline: Intermittent Iron and Folic Acid Supplementation in Menstruating Women.* Geneva, Switzerland: World Health Organization; 2011.

69. World Health Organization. Guideline: Intermittent Iron Supplementation for Preschool and School Age Children. e-Library of Evidence for Nutrition Actions (eLENA). Vol 2011. Geneva, Switzerland: World Health Organization; 2011.

70. De-Regil LM, Suchdev PS, Vist GE, Walleser S, Pena-Rosas JP. Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age. *Cochrane Database Syst Rev.* 2011;(9): CD008959.

71. World Health Organization. Use of Multiple Micronutrient Powders for Home Fortification of Foods Consumed by Pregnant Women. Geneva: World Health Organization; 2011.

72. Suchdev PS, De-Regil LM, Walleser S, et al. Multiple Micronutrient Powders for Home (Point of Use) Fortification of Foods in Pregnant Women: A Systematic Review. World Health Organization e-Library of Evidence for Nutrition Actions. Geneva, Switzerland: World Health Organization; 2011.

73. World Health Organization. Food and Agriculture Organization, United Nations Children's Fund, Global Alliance for Improved Nutrition, Micronutrient Initiative, Iour Fortification Initiative. Recommendations on Wheat and Maize Flour Fortification Meeting Report: Interim Consensus Statement. Vol 2012. Geneva, Switzerland: World Health Organization; 2009.

74. Pan American Health Organization. Guiding Principles for Complementary Feeding of the Breastfed Child. Washington, DC: Pan American Health Organization, World Health Organization; 2003.

75. World Health Organization. Preventative Chemotherapy in Human Helminthiasis. Coordinated Use of Antihelminthic Drugs in Control Interventions: A Manual for Health Professionals and Programme Managers. Geneva, Switzerland: World Health Organization; 2006.

76. De-Regil LM, Pena-Rosas JP, Flores-Ayala R, Jefferds ME. MED J. WHO/CDC logic model for micronutrient interventions in public health [abstract]. *FASEB J.* 2011;25(Meeting Abstract Supplement):108.1.

77. McDonald SJ, Middleton P. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. *Cochrane Database Syst Rev.* 2008(2): CD004074.