INACG Symposium
Why Iron Is Important and What to Do About It: A New Perspective

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This report is the summary of the presentations and discussions that took place at the INACG Symposium and does not necessarily reflect the scientific recommendations or views of INACG, the U.S. Agency for International Development, or the International Life Sciences Institute.

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INACG Symposium

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The INACG Symposium was hosted by INACG. The Office of Health, Infectious Disease and Nutrition, Bureau for Global Health, U.S. Agency for International Development, assumed major responsibility for organizing the meeting.

The INACG Secretariat gratefully acknowledges the additional contributions of the following organizations:

Kraft Foods, Inc.

The Local Organizing Committee for the XX IVACG Meeting

ABOUT INACG

The purpose of the International Nutritional Anemia Consultative Group (INACG) is to guide international activities aimed at reducing iron deficiency anemia (IDA) and other nutritionally preventable anemias worldwide. In fulfilling this mandate, INACG sponsors scientific reviews and convenes task force groups to analyze issues related to the etiology, treatment, and prevention of ID and IDA. INACG publishes guidelines and recommendations based on the work of these task force groups. Examination of these issues is important for the establishment of public policy and action programs.

INACG Publications

Iron Deficiency Anemia: Reexamining the Nature and Magnitude of the Public Health Problem (J Nutr Suppl 2001)

Safety of Iron Supplementation Programs in Malaria-endemic Regions (1999)

Guidelines for the Use of Iron Supplements to Prevent and Treat Iron Deficiency Anemia (1998)

The Effects of Iron Deficiency and Anemia on Mental and Motor Performance, Educational Achievement, and Behavior in Children - An Annotated Bibliography (1998)

Iron/Multi-Micronutrient Supplements for Young Children (1997)

The Oxford Brief - Child Development and Iron Deficiency (1997)

Iron EDTA for Food Fortification (Fact Sheet) (1997)

Iron EDTA for Food Fortification (1993)

Combating Iron Deficiency Anemia through Food Fortification Technology: An Action Plan (1992)

Lutte Contre l'Anémie Ferriprive par la Technologie de Fortification Alimentaire (1992)

Lucha Contra la Anemia por Deficiencia de Hierro Mediante Tecnología de Fortificatión de Alimentos (1992)

Guidelines for the Control of Maternal Nutritional Anemia (1989)

Lutte Contre l'Anémie Nutritionnelle Chez la Mere: Quelques Conseils (1990)

Pautas para el Control de la Anemia Nutricional en el Embarazo (1990)

La Lutte Contre la Carence en Fer: Etude de Cas Réalisé au Chili (1987)

Prevención de la Deficiencia de Hierro: La Experiencia de Chile (1987)

Measurements of Iron Status (1985)

Design and Analysis of Iron Supplementation Trials (1984)

Iron Deficiency in Women (1981)

Carence en Fer Chez la Femme (1983)

Deficiencia de Hierro en la Mujer (1985)

Iron Deficiency and Work Performance (1981)

Iron Deficiency in Infancy and Childhood (1979)

La Carence en Fer Chez le Nourrisson et Chez l'Enfant (1985)

Deficiencia de Hierro en la Infancia y la Niñez (1985)

Guidelines for the Eradication of Iron Deficiency Anemia (1977)

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The INACG Steering Committee composed of Drs. Suniti Acharya, John Beard, Frances R. Davidson, Lena Davidsson, Eva Hertrampf, Marian Jacobs, Sean Lynch, and Rebecca Stoltzfus planned the program and invited the individual speakers. These speakers who willingly shared their expertise contributed immeasurably to the symposium. The INACG Secretariat is grateful to the speakers for the papers that contributed to this report. The individuals who presented scientific and program posters during the INACG Symposium contributed to the richness of the meeting discussions and helped to build a worldwide network devoted to reducing iron deficiency anemia.

Drs. Sean Lynch and John Beard served as the rapporteurs for the meeting, generously offering their time and expertise to provide a comprehensive and insightful summary of the meeting for this publication. Drs. Lena Davidsson and Penelope Nestel provided careful review of the meeting report on behalf of the INACG Steering Committee.

Finally, the meeting participants were the true success of this event. They are the ones who hopefully gained key information needed to carry out vital programs for the reduction of iron deficiency anemia in their own countries.

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PROGRAM AT A GLANCE

2001 INACG Symposium

THURSDAY 15 FEBRUARY	FRIDAY 16 FEBRUARY
	0800-0900 Registration/Exhibits open
	0900-1000 **Developments in Assessment of Iron Status**
	1000-1030 Break and Poster Viewing
	1030-1130 **Prevention and Cure through Parasite Control Programs**
	1130–1230 **What to Do about Iron Deficiency:** **• Supplementation**
	1230-1430 Lunch and Poster Viewing 1430–1630 **What to Do about Iron Deficiency (continued):** **• Fortification** **Closing Remarks**
1600-1800 Registration for INACG Symposium Set up Friday's posters Set up INACG Exhibits	1630 End of INACG's Formal Sessions Remove Posters and Exhibits
1900-2100 INACG Symposium Opening Session **Keynote Address** **Why Iron is Important: Functional Outcomes of Iron Deficiency/Iron Deficiency Anemia**	

INACG Symposium Program

15-16 February 2001

Thursday, 15 February 2001

1600-1800	Registration Set up for Friday's posters Set up for exhibits
1900	**Opening Session** Co-Chairs: Dr. Lena Davidsson, Prof. Ha Huy Khoi
	Welcome Dr. Lena Davidsson
	Opening Remarks Dr. Frances Davidson
1915	**Keynote Address: Iron Deficiency/Iron Deficiency Anemia as a Public Health Problem in Developing Countries – Issues and Challenges for Policy Makers, Program Managers, and Scientists** Dr. Julia Tagwireyi
1945	**Why Iron Is Important – Functional Outcomes of Iron Deficiency/ Iron Deficiency Anemia**
1945	Pregnancy Outcome Dr. George Beaton
2005	Impact of Iron Deficiency/Iron Deficiency Anemia on Infant Behavior and Development Dr. Betsy Lozoff
2025	Discussion
2100	End of day's formal sessions

Friday, 16 February 2001

0800	Registration / Exhibits open
0900	**Developments in Assessment of Iron Status** Chair: Dr. Sean Lynch
0900	Epidemiological Assessment of Iron Status Dr. James Cook
0930	Discussion
1000	**Break and Poster Viewing**

Friday, 16 February 2001 (continued)

1030	**Prevention and Cure Through Parasite Control Programs** Chair: Dr. Rebecca Stoltzfus
1030	Malaria Dr. Malcolm Molyneux
1050	Helminths Dr. Lesley Drake
1110	Discussion
1130	**What to Do About Iron Deficiency–Supplementation** Chair: Dr. John Beard
1130	Iron Supplementation During Pregnancy and Lactation Dr. George Beaton
1150	Multi-Micronutrient Supplements Dr. Werner Schultink
1200	Discussion
1230	**Lunch and Poster Viewing/Guided Tours of Selected Posters**
1430	**What to Do About Iron Deficiency–Food Fortification** Chair: Dr. Lena Davidsson
1440	Food Fortification–An Overview Dr. Richard Hurrell
1500	Panel Discussion of Ongoing Food Fortification Programs Dr. Penelope Nestel Dr. Pham Van Thuy Dr. Eva Hertrampf Dr. Stanley Zlotkin
1520	Discussion
1600	**Closing Remarks** Dr. Lena Davidsson

End of INACG's formal sessions

1630	Remove posters and exhibits

2001 INACG Symposium, 15-16 February, Hanoi, Vietnam

International Nutritional Anemia Consultative Group

During the welcoming address of the 2001 INACG Symposium, Dr. Lena Davidsson, chair of the INACG Steering Committee, stressed the importance of designing effective strategies to combat the negative consequences of iron deficiency anemia, which are major public health problems. Dr. Frances Davidson, INACG secretary, reiterated the commitment that the U.S. Agency for International Development has to improving the iron status of women and children in developing countries. Dr. Davidson emphasized that iron deficiency is the world's most prevalent micronutrient deficiency, yet little attention has been given to preventing and combating iron deficiency and iron deficiency anemia. She was pleased that the interest in iron deficiency is growing and that a constituency is beginning to form around iron, much like the constituency that vitamin A has benefited from.

Introduction

Keynote Address: Iron Deficiency Anemia As A Public Health Problem

Ms. Julia Tagwireyi, Head of the Nutrition Unit, Ministry of Health and Child Services, Harare, Zimbabwe, discussed issues and challenges for policy makers, program managers, and scientists in implementing programs to reduce the prevalence of iron deficiency (ID) and iron deficiency anemia (IDA). ID is the most prevalent micronutrient disorder in the world, and extrapolating from 1985 data, IDA affects as many as 600 to 800 million people (Ross and Horton 1998). Women of reproductive age, preschool children, and adolescent girls are affected most, but other groups, including men, are not exempt from risk.

The main causes of iron deficiency are:

- a diet deficient in bioavailable iron
- increased requirements for iron, e.g., during pregnancy
- losses of iron due to parasite infections.

Compounding the negative effects of these conditions is the fact that they often coexist. The consequences of IDA are serious and can include diminished intellectual and productive capacity and increased susceptibility to infections. A recent analysis of the economic consequences of IDA estimated productivity losses to be 0.9% of the Gross Domestic Product (GDP) in developing countries (Ross and Horton 1998).

Current approaches to controlling ID and IDA include promoting the increased intake of foods rich in bioavailable iron or factors that enhance the bioavailability of iron, food fortification, supplementation, and the control of parasitic infections. These approaches, however, are often constrained because food security initiatives focus on macronutrients and micronutrients such as iron are often forgotten. Policies, institutional frameworks, or comprehensive national strategies that address micronutrients often do not exist. Also, leadership to manage the programs for reducing nutritional anemias and to be held accountable for their success is frequently lacking. In addition, scientists, policy makers, and program managers are not cooperating effectively to resolve problems at the operational level. As a result, inadequate training and attention has been given to translating scientific discovery and current knowledge about ID and IDA into effective program action.

Effective nutritional anemia control programs require a comprehensive advocacy strategy that targets policy makers, program planners (including economists), and recipients to deliver clear messages that motivate behavior change. Monitoring program quality and effectiveness is another critical component of successful public health programs. However, developing countries often lack the resources needed for

All contents and ideas presented in these papers are the work of the authors and do not necessarily reflect those of INACG, USAID or the International Life Sciences Institute.

monitoring and evaluating supplementation and food fortification programs. In addition, key elements in planning food fortification programs, such as food consumption data are often incomplete.

Effective action to control iron deficiency has been problematic in part because nutrition and health issues have been sidelined on the development agenda. Moreover, ID and IDA have been approached mainly from a medical perspective and key players from other development sectors, whose active participation could aid in alleviating the problem, have been excluded. For example, the effectiveness of parasite control programs to alleviate anemia has been limited by the lack of integration with nutrition interventions such as the delivery of iron supplements, which has been confined to the health sector. As public sector health resources diminish, iron supplements, and even paracetamol, have become scarce in government clinics. Alternative delivery systems supported by institutional frameworks must be sought if they are to become sustainable. Also, involving non-medical specialists, such as economists, is critical to influencing and changing the behavior of policy makers who will make decisions regarding the control of ID and IDA.

Controlling ID and IDA poses many challenges, for example, the increasing rate of poverty, which further reduces the options available to poor people acquiring their basic nutrition requirements. Poverty also limits a nation's capacity to implement and improve the existing food, nutrition, and health programs. HIV-AIDS poses another challenge, especially in sub-Saharan Africa. The effect on nutritional status or the implications for case management if iron supplementation potentially exacerbates the problem of opportunistic infections cannot be ignored. Additionally, because women produce 60% of the food in Africa, a reduction in their work capacity will compromise food security for all.

To overcome these challenges the following action is needed:

- promote optimal nutrition in the wake of increasing poverty and HIV/AIDS
- improve the effectiveness of current strategies in the wake of deteriorating infrastructure, diminishing access to resources, and inadequate human capacity
- identify alternative delivery systems that engage communities and do not rely on the health sector alone.

Iron deficiency anemia is not only a public health problem, but also a development problem. Its prevention and reduction must be viewed as investment in human capital that will enhance development and reduce poverty. To control nutritional anemia, developing countries should:

- Establish policy and institutional frameworks that embrace a multi-sector approach
- Develop strategic alliances and partnerships with key stakeholders in the public and private sectors and define their roles and accountability in the control of iron deficiency anemia
- Adopt a lifecycle approach to controlling ID and IDA that includes the promotion of optimal nutrition
- Improve ID and IDA prevention and reduction programs' effectiveness by identifying existing constraints and addressing them
- Develop a behavior change strategy targeted to policy makers and program managers, so that they respond to strategies for reducing anemia and to communities to empower them to act on their problem
- Strengthen and develop the human capacity to effectively implement the plethora of interventions that are needed to control iron deficiency anemia.

It is scandalous that iron deficiency anemia continues unabated despite knowledge of reliable measures to prevent and manage it effectively. Its existence must no longer be tolerated; the challenges are many, but something can and must be done with the existing body of knowledge.

WHY IRON IS IMPORTANT

Functional Outcomes of Iron Deficiency and Iron Deficiency Anemia in Pregnancy and Beyond

Dr. George Beaton, University of Toronto, Ontario, Canada, discussed the evidence of a causal relationship between iron deficiency (ID) and iron deficiency anemia (IDA) and maternal mortality, maternal morbidity, as well as pregnancy outcome.

Background

Much has been written about the consequences of iron deficiency and the presumed functional benefits of intervention. Some work cited in advocacy statements is very new; much is quite old. And, like so much else in nutrition, much information, because we have heard it so often, is accepted as valid without critical examination. In recent years however, we have been challenged to reappraise the actual problems we are trying to address with our interventions. Here we will examine the effects of ID and IDA, not only in pregnancy, but also beyond, to emphasize the need for careful and critical reassessment of the actual public health problems and what might be expected from iron supplementation.

The Unfolding Story

The beginning of the reevaluation of anemia in pregnancy is difficult to identify. There were major transatlantic disputes in the 1960s about functional effects of anemia in pregnancy and desirable target hemoglobin concentrations, but these gradually subsided. Since then, single questioning voices have been heard periodically. A clear and salient marker of the current plea for reexamination of evidence and reconsideration of assumptions was the review of anemia and maternal mortality and pregnancy outcomes by Dr. David Rush, which was featured in a 1998 OMNI Research meeting (Rush 2000). Rush found evidence of relationships between severe anemia and mortality but not evidence that established the direction of the association or specifically linked the relationships to iron deficiency. He strongly challenged the accepted nutritional dogma that portrayed maternal mortality (and low birth weight) as a risk of iron deficiency and mild anemia. At that same meeting, van den Broek and Letsky (van den Broek and Letsky 2000) demonstrated that among 150 pregnant women in south Malawi, with moderate or severe anemia, only 53% showed biochemical evidence of any iron deficiency, with or without other micronutrient deficiencies; 26% were not deficient in iron but showed evidence of one or more other micronutrient deficiencies; 19% showed no evidence of any micronutrient deficiency that was examined. These were studies of association without inference of causation. The authors (van den Broek and Letsky 2000) suggested that chronic inflammation was likely to have been an important cause of anemia in these women. Again in that meeting, Beaton (Beaton 2000) pointed out that the existing World Health Organization (WHO) criteria of anemia in pregnancy appeared to reflect the maximal hemoglobin levels that could be achieved among healthy, iron-supplemented women in the industrialized world. He noted also that the WHO criteria did not reflect the well-documented changes in hemoglobin that occur during pregnancy as documented by R. Yip (Centers for Disease Control and Prevention 1989). Beaton emphasized the absence of functional evidence to support the WHO criteria. In fact, he noted that setting out to achieve the WHO target hemoglobin levels instead of preventing moderate anemia might double the level of the dietary iron requirement, leading to the immediate conclusion that pharmaceutical supplementation is mandatory. The implications for programming seem obvious.

A more recent INACG/WHO meeting at the Belmont House near Baltimore, Maryland, USA (Beard and Stoltfuz 2001), convened a group of experts to review specific areas of

function that have been alleged to be associated with iron deficiency. The areas of function examined included:

- maternal mortality
- birth weight and perinatal mortality
- immunity and infectious disease
- child mortality
- cognitive development
- work capacity and performance.

For each area, the reviewers were asked to address three questions:

a) Is there clear evidence of an association between the area of function and anemia?

b) If so, at what level of severity of anemia can the association be demonstrated?

c) Is there evidence that the function is explicitly linked to iron deficiency rather than to the anemia regardless of cause?

The group agreed that for work capacity and performance and child development (formerly identified as cognitive development), the evidence was convincing for a causal association between severe anemia and function. The associations appeared to extend through at least moderate anemia.[1] There were hints, but not clear evidence, that the associations might extend into the range of mild anemia. Estimating the possible effects of mild anemia on human behaviors (child development or work performance and endurance) was extremely difficult because many other variables (for example, social factors) are known to influence the outcome measures and confound analyses.

In examining maternal and child mortality and infectious disease, there was strong evidence of an association between severe anemia and the outcome measure. However, evidence pertaining to the direction of causality was inconsistent and inconclusive. Conclusions drawn depended more on judgment and opinion than firm evidence. The evidence relating these outcomes to ID per se was even more tenuous.

In the examination of reported associations between anemia and birth weight, prematurity, and perinatal mortality, it was concluded that available evidence was unconvincing because of limitations of the design of reported studies. Although an association with severe anemia and these outcomes seemed consistent, there was no evidence to attribute this association to iron deficiency. The reviewer concluded that available evidence from this set of pregnancy outcomes was insufficient to either accept or refute the widely hypothesized associations of birth weight, prematurity, and perinatal mortality with iron deficiency.

Where does that leave scientists studying the evidence? Evidence exists that shows where severe, and perhaps moderate anemia are prevalent, there are likely to be functional associates that should be of public health concern. However, with the exception of work capacity and performance and cognitive development, scientists cannot be sure of the direction of causation. Even for these two areas, whether iron deficiency is a direct associate of function or a contributing cause of anemia, although the former would seem logical on the basis of present biological knowledge, is not certain. For the other areas of function, evidence exists that shows only that impairment is more likely to be seen among individuals with severe and possibly, moderately severe anemia.

When Beaton and McCabe (Beaton and McCabe 2002) conducted their comparative analysis of daily and intermittent iron supplementation, both were found to be efficacious but, perhaps more importantly, even in these field research studies where motivation to comply would be expected to be higher than in operational programs, the authors concluded that neither route of administration appeared very effective. In a substantial number of these trials, the prevalence of anemia remained in the WHO-defined range of a major public health problem at the end of the trials. It has been repeatedly reported for operational

[1] In this section of the report, severe anemia in pregnant women is defined as hemoglobin below 70 g/L; moderately severe anemia is defined as hemoglobin between 90 and 70 g/L; mild anemia is defined as hemoglobin between 110 and 90 g/L.

programs: *iron supplementation doesn't work*. Program failure is often attributed to inadequate infrastructure and/or poor compliance. Beaton challenges those assumptions as the main explanation for program failure. Instead, he suggests that existing programs might be more effective than previously thought and the problem is two-fold:

1) inappropriate and unnecessarily high, perhaps unachievable, targets have been adopted
2) the assumption that a primary iron deficiency exists may be incorrect in many field situations.

On the issue of international goals, it was noted above that the criteria of anemia in pregnancy were set on grounds that cannot be defended as functionally essential. The reviews at the Belmont meeting (Beard and Stoltfuz 2001) support that conclusion; for pregnancy at least, it appears that there is no *demonstrable* benefit in reducing the prevalence of mild anemia while there would be an expected (albeit not established) benefit of controlling severe and perhaps moderate anemia of all causes. As Table 1 illustrates for the pregnancy trials examined by Beaton and McCabe (Beaton and McCabe 2002), the inference of success or failure would be very different if the goal was seen as control of moderate anemia (Hb <90 g/L) instead of control of mild anemia as defined by the existing WHO criteria (Hb <110 g/L). Is it possible then that existing programs are much more effective than previously concluded? It is difficult to know since few reports include estimates of the prevalence of moderate anemia or provide information about effects on the distribution of hemoglobin levels.

Van den Broek and Letsky (van den Broek and Letsky 2000) suggested that among anemic, pregnant women in south Malawi, only 53% showed biochemical evidence of iron deficiency. That is the maximum proportion of people among whom anemia could be expected to respond to the administration of iron. For those supplementation research studies examined by Beaton and McCabe that included a control group (none of the pregnancy studies included a control group) it is possible to derive a crude estimate of the proportion of anemia that was attributable to iron deficiency seen by a response to iron-folate supplementation. The derived estimates are shown in Table 2.

Table 1. Impact of criterion of anemia on the apparent prevalence of anemia and success of daily iron supplementation during pregnancy.

	Prevalence of Anemia during pregnancy	
Criterion of Anemia	Baseline	Post Intervention
Mild Anemia* <110 g/L	39 %	32.3 %
Moderate Anemia* < 90 g /L	6.7 %	3.1 %

Pooled data from 4 studies,n = 750
Derived from Beaton and McCabe (Beaton and McCabe 2002)
*WHO criteria from Stoltzfus (Stoltzfus and Dreyfuss 1998)

It can be shown that the van den Broek and Letsky (van den Broek and Letsky 2000) data would overestimate the proportion of the initial anemia *attributable* to iron deficiency since they demonstrated coexistence not causation. The estimates derived from Beaton and McCabe (Beaton and McCabe 2002) are likely to be underestimates of the *attributable*

Table 2. Estimated proportion of anemia attributable to iron deficiency.

Location	Age Group	Estimated Attribution
Baroda	Adolescents	26 %
Bombay	Adolescents	55 %
Delhi	Adolescents	41 %
East Jakarta	Adolescents	63 %
La Paz	School children	84 %
Mali	Adolescents	21 %
Peru	School children	52 %
Sri Lanka	Adolescents	36 %
Vietnam	Preschool children	85 %

Derived from Beaton and McCabe (Beaton and McCabe 2002) including only studies that had a control group. None of the pregnancy studies included control groups.

proportion simply because they were finite in duration—continuation for longer times might have resulted in greater response. Nevertheless, the main conclusion seems clear: A considerable proportion of the observed anemia is not likely to be responsive to iron alone or iron-folate. If control of anemia is the real objective of public health programs, then the need for more comprehensive approaches must be considered. The problem can no longer be seen as being one of only iron deficiency anemia. There is no question that iron deficiency is a major contributor to anemia and its functional consequences, but it is not the only contributor and may not be the most limiting factor in all situations.

Suggested Implications

In the closing discussions of the Belmont meeting (Beard and Stoltzfus, 2001), de Benoist commented (page 701s), "The problem with iron deficiency is that first we have to demonstrate that it is a public health problem." In that same discussion, Habicht commented (page 701s), "[The major contribution of this meeting is that] this is the first time we sat down and looked at the functional outcomes." Together, these comments summarize the current situation regarding iron deficiency and anemia. We must therefore take the time and effort to define explicitly, in functional terms, the precise problem to be addressed and the actual expectations for intervention programs. David Rush (Rush 2000) deserves much credit for raising the issue of the need for revised thinking about iron deficiency and anemia to a level that demands attention. The impact of this revised thinking on the definition of the public health problem and possible strategies to alleviate it was exemplified in a recent meeting in Bangladesh (Boy Gallego 2000), which arose from Rush's arguments.

These considerations have major import in the setting of national and international targets and goals for control of anemia prevalence, if indeed the setting of goals is accepted as desirable (United Nations ACC/Subcommittee on Nutrition 2001). The questions that have arisen in the recent revaluations of accepted dogma also carry obvious implications for future research needs and for the future role of INACG. That consultative group is well positioned to accept and fulfill a major role in a careful, objective re-evaluation of function-based criteria for the definition of anemia and "diagnosis" of problems in the field as a basis for the design and evaluation of operational programs.

Unless and until this reevaluation is done, iron deficiency anemia is unlikely to attract major attention among donors and national ministries of health. There is an urgent need for rethinking.

Discussion

In answering questions from the audience, Dr. Beaton confirmed his suggestion that no more than half of all anemias in the world are actually due to iron deficiency. Dr. Mary Cogswell, U.S. Centers for Disease Control and Prevention, emphasized the need to think of anemia in terms of the timing and duration during pregnancy. Some women in intervention trials may be identified and supplemented after a very short period of anemia, while others may be in an anemic state for a much longer period of time before being supplemented. These differences in "exposure" to anemia will confound the interpretation of any apparent effects of iron supplementation.

Dr. Cogswell stated that timing in relation to fetal growth might also be important. Fetal length increases most rapidly at the end of the first trimester, while fetal weight increases most rapidly at the end of the second trimester. Two poster presentations (#7 and #8) at the 2001 INACG Symposium reported results from a randomized, controlled trial of iron supplementation to non-anemic, iron-replete women. The findings highlight the importance of adequate iron stores early in pregnancy and adequate iron intake during pregnancy to prevent adverse birth outcomes.

Dr. Beaton reminded the audience that the timing of hemoglobin measurements is

poorly controlled in most reported studies. This is a major problem because of the known physiological variation in hemoglobin levels during pregnancy. A review of 23 interventions by Rasmussen (Rasmussen 2001) failed to document a causal association between maternal hemoglobin and birth weight or a specific association with iron deficiency anemia. She noted that there was an inherent design bias in these studies against finding a positive result. Therefore, one could not rule out such a relationship.

Dr. Bernard Brabin, Liverpool School of Tropical Medicine, offered his view that fetal anemia is common in many sub-Saharan African countries, even when the mother is not severely anemic. Cross-sectional studies in developing countries show a significant correlation between maternal and fetal (measured using cord blood) hemoglobin levels. Verhoeff and her colleagues in Malawi (Verhoeff 1999a) have demonstrated that fetal anemia (based on cord blood measurement) is related to seasonal patterns of malaria that effect maternal hemoglobin at delivery and maternal iron status. There is a relationship between maternal anemia and anemia in the infant at birth. Verhoeff et al. (Verhoeff 1999b) also found a clear correlation between cord blood hemoglobin, infant birth hemoglobin and risk of anemia at six months of age. Dr. Brabin suggested that fetal anemia and iron deficiency at birth could have important effects on early mental development.

Impact of Iron Deficiency and Iron Deficiency Anemia on Infant Behavior and Development

Dr. Betsy Lozoff, Center for Human Growth and Development, University of Michigan, Ann Arbor, USA, discussed the effect of iron deficiency (ID) and iron deficiency anemia (IDA) in early life on behavior and development. Studies contrasting infants with iron-deficiency anemia to a comparison group generally find lower mental and motor test scores and other behavioral differences in the iron-deficient anemic subjects. Results after iron therapy vary, and only one study showed complete correction of test score differences in infancy. Most studies report persistent differences, even in the long-term.

The longest follow-up study, done in Costa Rica (Lozoff et al. 2000), reevaluated 87% of the original 191 children who had been tested and treated in infancy for iron deficiency (defined as a low ferritin level and 1 other abnormal iron measure) at 11-14 years of age (average age = 12.3 years). Those who had chronic, severe iron deficiency in infancy (n = 48) were compared with those who had good iron status before and/or after iron therapy in infancy (n = 114) on a comprehensive set of cognitive, socio-emotional, motor tests, and measures of school functioning. The group with chronic, severe iron deficiency were children whose hematology in infancy showed iron deficiency and hemoglobin =100g/L or a higher hemoglobin level but abnormal iron measure(s) after three months of iron therapy. Children who had severe, chronic iron deficiency in infancy scored lower on measures of mental and motor functioning. After controlling for background factors, differences remained statistically significant in arithmetic achievement, written expression, motor functioning, and some specific cognitive processes—spatial memory, selective recall, and tachistoscopic threshold. More of the formerly iron-deficient children had repeated a grade and/or had been referred for special services or tutoring. Their parents and teachers rated their behavior as more problematic in several areas, including anxiety and/or depression, social problems, and attention problems. Thus, severe, chronic iron deficiency in infancy identified children who continue at developmental and behavioral risk more than 10 years after iron treatment.

These results suggest either that iron-deficiency anemia in infancy has effects that cannot readily be corrected with treatment, as in the rat model, or that other factors are the cause of poorer behavior and development. Although the most powerful

way to deal with such factors is through a randomized controlled trial in which iron deficiency is experimentally prevented in some infants but not in others, no consistent pattern of results has emerged from the 3 published, preventive trials in full-term healthy infants. (Moffatt et al. 1994, Williams et al. 1999, Morley et al. 1999).

Lozoff et al. recently completed analysis of another large double-blind supplementation trial, involving 1657 healthy full-term Chilean infants who were randomly assigned to recent high, low, or no-added iron conditions between 6 and 12 months of age (Lozoff et al. 2001). At 12 months iron-deficiency anemia was present in 2.5%, 4.0%, and 22.6% of the high-, low-, and no-added-iron groups, respectively. There were effects of iron supplementation, whether high- or low-iron, on specific behavioral/developmental outcomes. Infants who received supplemental iron crawled earlier and were less likely to be tremulous. They processed information faster. A greater proportion of them resisted giving up toys and test materials, but could be soothed by words or objects when upset. They were more likely to show positive affect, interact socially, and check their caregivers' reactions. There were no differences in global test scores. The study shows that healthy, full-term infants may receive developmental and behavioral benefits from iron supplementation in the first year of life.

These results and those of other new studies seem to fit with recent research on iron deficiency and the developing brain. Iron is required for many relevant central nervous system processes, the most studied being myelination and dopaminergic functioning. Systems that are rapidly myelinating during the period of iron deficiency might be especially vulnerable. A later age at which a child begins crawling could be congruent with a delay or disruption in myelination. Any process that reduces the speed of neurotransmission could also result in longer looking times on the Fagan test.

Recent neurophysiologic studies provide more direct evidence of the effects of iron deficiency on the developing brain. Evoked potentials are a noninvasive means of examining aspects of the central nervous system (CNS). Auditory brainstem responses (ABRs) represent the progressive activation of the auditory pathway from the acoustic nerve (wave I) to the lateral lemniscus (wave V). The central conduction time (CCT) or wave I-V interpeak latency is considered an index of CNS development because myelination of nerve fibers and maturation of synaptic relays lead to an exponential reduction in the CCT from birth to 24 months. In 55 otherwise healthy, 6-month-old Chilean infants (29 with iron deficiency anemia and 26 nonanemic control infants), the CCT was longer in those who had been anemic at 6 months, with differences becoming more pronounced at 12- and 18-month follow-ups despite effective iron therapy (Roncagliolo et al. 1998).

To determine long-term effects of IDA in infancy on nerve conduction in sensory systems, we compared 3- to 4-year-old Chilean children who were treated for IDA or were nonanemic in infancy on ABRs and/or visual evoked potentials (VEPs) (Algarin et al. 2001). Absolute latencies for all ABR waves and inter-peak latencies were slower in former IDA children. The magnitude of effects was large–about 1 SD, as observed in the infancy study. Large magnitude differences in latencies were also observed for VEPs. Thus, despite iron therapy in infancy, there were long-lasting delays in nerve conduction velocity in 2 sensory systems that rapidly mature during the period of iron deficiency. Differences in latencies, but not amplitudes, suggest that impaired myelination is the explanation for the altered auditory and visual messages. Subtle changes in transmission might be an underlying mechanism for interference with other aspects of development in early IDA, and impaired myelination more generally could contribute to poor outcome.

Early iron deficiency also adversely affects dopaminergic neurotransmission. Altered dopaminergic functioning is a known factor in extraneous motor movements, such as

tremor. Tremor was observed in more of the non-iron-supplemented group in the Chilean preventive trial. Dopamine also plays an important role in the degree to which individuals experience inherent reward. The behavioral differences in the non-iron-supplemented group in the preventive trial (and in previous case-control studies) appear to indicate less positive responsiveness to the physical and social environment.

In sum, recent studies support the relationship between early IDA and poorer behavior and development. The specific findings are consonant with the current understanding of iron's role in the developing brain.

Discussion

Questions from the audience addressed whether the association for deficits in mental and motor development is with iron deficiency or iron deficiency anemia. If associated with iron deficiency, why are these problems not more prominent in western countries that do not endorse iron supplementation in early infancy? Dr. Stanley Zlotkin, The Hospital for Sick Children, Toronto, pointed out that in Canada, 25-30% of infants are iron deficient as defined by low serum ferritin. Dr. Lozoff stressed that the findings of altered transmission in sensory systems were in Chilean children who had been anemic and iron deficient. The sample size did not permit evaluation of iron deficient and iron deficient anemic infants separately.

In response to a question about the age of onset of iron deficiency and duration of the condition, Dr. Lozoff replied that timing, duration, and severity were intimately intertwined. Infant studies have not been able to address these issues directly. Such studies are only possible in animal models. However, in the evoked potential follow-up study, where observations were made at age 3-4 years, slower transmission was observed regardless of the age in infancy at which IDA had originally been identified, i.e., six, twelve, and eighteen months of age. Relationships to severity are also not clear.

With overall developmental measures, there appeared to be a threshold level of anemia that was necessary to find effects. This may not be the case if more sensitive measures are used.

Dr. Lozoff agreed with a participant who argued that evaluating the effects of iron deficiency in school-aged children could be confounded by the long-lasting effects of prior iron deficiency irrespective of their iron status at the time of follow-up testing. Iron deficiency at different ages could have different effects, some of which may be reversible and others not. These differences may explain the differences in reversibility reported in the literature.

Prenatal iron deficiency may affect brain development at an even earlier age than six months. Dr. Lozoff agreed that the old medical school teaching that the baby is protected from iron deficiency in an iron-deficient mother is probably wrong. Understanding the functional impact of fetal iron deficiency and early infant iron deficiency should be high priority for research.

Dr. Lozoff mentioned that there are several ongoing supplementation trials during pregnancy that will evaluate infant outcome in terms of infant development. Results should be available soon and may provide evidence of causality.

In response to a question about iron status of breast-fed infants, Dr. Lozoff agreed that breast milk alone might not meet the baby's needs for iron after about six months of age. In Chilean observational studies, 25-30% of breastfed infants had IDA by nine months. In the final years of the supplementation study, babies were randomly assigned to the study groups irrespective of feeding pattern. The group receiving no-added-iron included both breastfed and non-breastfed infants. The poorer behavioral and developmental outcome observed in this group could not be related to whether the infants were breastfed or not.

When asked to suggest indicators of developmental outcome that could be

measured in a program setting, Dr. Lozoff responded that testing babies is not simple. Her suggestion was the Fagan test (Fagan and Singer 1983), but this non-routine test requires considerable sophistication of the testing staff and is quite costly.

Dr. Lozoff explained that the influence of other micronutrient deficiencies on developmental outcomes in the studies she reviewed was less likely, because the overall nutritional status of the Costa Rican and Chilean infants was good. Infant mortality was low and there was no growth failure. In the Chilean supplementation trial, babies were given fortified commercial infant formula or vitamins if breastfed. Thus, unidentified micronutrient deficiencies were not likely to have influenced the results.

Dr. Zlotkin called for development of 'sound bites' that describe these practical consequences of iron deficiency in infancy for use in advocacy programs. Dr. Lozoff suggested that the effects on the infant's social-emotional development might be at least as important as its effects on the infant's cognitive development.

DEVELOPMENTS IN ASSESSMENT OF IRON STATUS

Epidemiological Assessment of Iron Status

Dr. James Cook, Department of Hematology, University of Kansas Medical Center, Kansas City, USA, discussed assessing iron status, including the usefulness of using anemia as an accurate indicator of iron deficiency.

Iron deficiency (ID) in humans was originally recognized by the anemia accompanying its late stages. Unfortunately, the assumption that anemia is synonymous with iron deficiency has persisted to the present time. While anemia provides a useful index of the severity of iron deficiency, the hemoglobin determination has serious limitations as a screen for iron deficiency. The major problem is the extensive overlap in hemoglobin values between normal population and those individuals with iron deficiency anemia (IDA) (Cook et al. 1971, Cook et al. 1976). Moreover, the hemoglobin criteria for anemia varies with age, sex, geographic area, and racial background. Another important limitation of using anemia to screen for iron deficiency is that there are many other causes of anemia, especially in countries where there is a high prevalence of infection or inflammatory disorders (Staubli Asobayire et al. 2001). Fortunately, there are newer, more effective methods of screening for iron deficiency.

The detection of IDA is relatively straightforward when the population is healthy and infection is uncommon. The optimal laboratory approach is to use the serum ferritin (SF) to measure iron stores, the serum transferrin receptor (sTfR) to assess tissue iron supply, and the hemoglobin to identify anemia. Three categories of iron status can then be defined: iron repletion when all measurements are normal, iron deficiency when the SF is low and the sTfR elevated, and iron deficiency anemia when hemoglobin indicates anemia. Even the hemoglobin can be deleted from this laboratory profile. When serial phlebotomies were performed in normal subjects, the ratio of sTfR/SF was found to correlate with body iron over a wide spectrum of iron status (Skikne et al. 1990). This ratio is especially valuable for quantifying the changes in body iron resulting from various intervention strategies.

The detection of IDA is far more difficult in populations where anemia is multi-factorial and especially when infections are common. The specificity of low hemoglobin is further reduced and the usefulness of the SF is limited because the concentration is falsely elevated by acute or chronic inflammation. Fortunately, the assay of sTfR remains valid because it is not affected by inflammation or infection and can therefore identify IDA even in subjects with concurrent infection (Ferguson et al. 1992, Punnonen et al. 1997).

The optimal approach for assessing iron status when inflammatory disorders are common has not been established. The definitive method involves bone marrow examinations that are obviously impractical. Another method is to exclude all subjects with laboratory evidence of associated disease. For example, those with chronic inflammation can be excluded using either the C-reactive protein or erythrocyte sedimentation rate and specific infections such as malaria or HIV can be identified using appropriate laboratory measurements. Another approach is to use the hemoglobin response to iron therapy as an index of IDA. However, reliable data requires supervised administration of the iron, an approach that is costly and cumbersome. Clearly, there is a need to develop more effective methods for identifying IDA in populations where anemia is multi-factorial.

Discussion

Dr. Cook addressed a number of questions from the audience that dealt with the difficulties encountered in using hemoglobin values to evaluate iron status, technical issues related to the use of SF and sTfR measurements, and possible approaches to define iron status in the presence of inflammation.

Dr. Abe Parvanta, U.S. Centers for Disease Control and Prevention, pointed out that the hemoglobin cutoff levels used in the United States represented the fifth percentile of values measured in the National Health and Nutrition Examination Survey (NHANES). The World Health Organization values have stood the test of time, but there are geographical, racial differences, including inherited blood disorders, and gender that may affect the range of normal hemoglobin values according to Dr. Cook. He suggested using mixed distribution analyses on large samples to address this issue.

Dr. Bo Lonnerdal, University of California at Davis, pointed out problems with using hemoglobin response to iron administration as a measure of iron deficiency in infants. Data reported on his poster (#22), showed that administration of iron to infants 4–6 months of age in both Honduras and Sweden caused a marked upward shift in hemoglobin values. The basal iron status in Honduran children was suboptimal, but in Sweden it was excellent. From 6–9 months of age, however, only the Honduran children showed an increase in hemoglobin concentration. However, major differences in the intake of fortified foods exist between the countries, which will be important in determining the outcome in the older infants.

Dr. Lonnerdal referred to an unpublished stable isotope absorption study (Domellof et al. in press) that showed that iron absorption was unrelated to iron status between 4 and 6 months of age. After six months of age, the control mechanisms for iron absorption start to mature and by nine months of age, absorption is related to iron status. Based on these data, Dr. Lonnerdal concluded that hemoglobin distribution is unlikely to be helpful to evaluate the impact of additional iron before six months of age.

Dr. Cook stated that it is unlikely that malaria alone will shift the hemoglobin distribution curve. A variety of undefined inflammatory causes are more likely to shift the curve, for example, where HIV is common and where individuals are susceptible to a wide variety of infections. The C-reactive protein is the most useful screening tool for identifying the presence of the inflammatory processes. In Asia, thalassemias may also be important, as these inherited disorders may alter hemoglobin distributions. More research is needed to quantify their impact.

Because SF values are affected by inflammation, Dr. Cook suggested that if the prevalence of SF values below 15 μg/L was low then inflammation should be suspected. At present there is no good validation for use of higher SF cut-off values to identify iron deficiency. Serum transferrin receptor levels may be a better indicator in populations with high levels of inflammation, and this has been established in a study in the Ivory Coast (Staubli Asobayire et al. 2001).

Another participant suggested that alpha-1-acid-glycoprotein stays elevated longer than CRP and may be much better for evaluating the effect of inflammation on SF levels. When asked about the time course for elevation of CRP compared to that of SF, Dr. Cook said that the rise in SF probably lasts longer. Inflammation causes a build-up of SF in macrophages, which then must be cleared. Post-operatively, it may take 4-6 weeks for SF levels to return to the pre-operative level.

When asked about standardization of sTfR assays, Dr. Cook said that the commercially available kits contain internal standards. However, it was noted that at present there is no way to standardize findings across studies. If the sTfR is used to estimate body iron, the assay employed must be calibrated by phlebotomy studies in human subjects (Skikne et al. 1990).

The usefulness of sTfR levels to measure iron status in young infants was raised. Dr. Cook noted that more research on this age group is needed to better define cut off levels during early life. In addition, the usefulness of sTfR concentration during periods of expansion of red blood cell mass due to rapid growth or malaria for example, needs to be evaluated.

Cost issues were raised. The cost of measuring hemoglobin concentration is inexpensive while more sophisticated techniques such as enzyme-linked immuno assay (ELISA), which is used for SF and sTfR, are more expensive. A careful evaluation of the cost in relation to the information obtained is important when comparing the costs of assays.

PREVENTION AND CURE THROUGH PARASITIC CONTROL PROGRAMS

The Potential Impact of Malaria Control on Anemia in Populations Where Malaria is Endemic

Dr. Malcolm Molyneux, Malawi-Liverpool-Wellcome Trust Clinical Research Program, Universities of Malawi and Liverpool, Blantyre City, Malawi, discussed the importance of malaria control to reduce the prevalence of anemia. Dr. Molyneux pointed out that several lines of evidence indicate that malaria is an important cause of anemia in malaria-endemic areas. Clinical evidence shows that individuals with malaria infections commonly become anemic, sometimes severely anemic (see Table 3 for possible mechanisms). This is evident in routine clinical practice and was observed in pre-penicillin days when malaria was inoculated to induce fever in the treatment of syphilis (O'Leary 1927). Treatment of malaria usually results in correction of anemia, and ineffective treatment of malaria is commonly accompanied by persisting anemia (Phillips and Pasvol 1992).

Epidemiological Evidence

Epidemiological evidence suggests that in endemic areas the population groups most susceptible to malaria–children and pregnant women–are also those with the greatest burden of anemia (Schellenberg et al. 1999). In such areas there is an association between *P falciparum* parasitemia and anemia, and both of these are increased in seasons of increased malaria transmission (Verhoeff et al. 1999b; Rogerson et al. 2000b). In one study, placental parasitemia and maternal anemia were less prevalent among women who had taken presumptive antimalarial treatment than among those who had not (Rogerson et al. 2000a). Drawing conclusions from epidemiological evidence is unreliable because of confounding factors. Thus, malaria transmission tends to coincide geographically both with poverty in general and with other factors, such as geohelminth infections and nutritional deficiencies, which may contribute to anemia in a population.

The importance of malaria as a contributor to the burden of anemia in a population can only be assessed confidently through interventions that specifically target malaria in a randomized manner. Such interventions not only constitute a tool by which to assess the causes of anemia, but also provide an additional potential means of anemia control. Evidence for the importance of malaria as a contributor to anemia in populations comes from randomized controlled trials of interventions directed against malaria, namely insecticide treated bed nets (ITBN), also known as impregnated bed nets, and antimalarial drug chemoprophylaxis studies.

Several well-conducted trials of ITBN in malarial areas have now demonstrated that the use of nets can reduce malaria in a community as measured by *mortality* in young children, prevalence of parasitemia, and incidence of symptomatic infections (Lengeler 1998). Many of these studies have also shown a concomitant decrease in the incidence of anemia and an increase in the population's mean hemoglobin (Hb) concentration among bed net users. For example, in a recent study in western Kenya, the incidence of anemia (packed cell volume (pcv) < 30%) among 167 pregnant women living in villages provided with ITBNs was 376 per thousand woman-months, compared with 455 per thousand among 182 women in control villages ($p<0.0005$) (Ter Kuile, F., personal communication 2001). In a Gambian study, the mean pcv in 300 children in villages without bed nets fell after the malaria season from 32.9% to 30.6%, the mean fall being 2.41%; in 357 children in villages using bed nets, the fall was significantly less, from 32.7% to 32.2%, with a mean fall of 0.52% (Alonso et al. 1993).

Both malaria chemoprophylaxis and intermittent, presumptive treatment of malaria during pregnancy have been shown to result in improved maternal hemoglobin concentrations (McGregor 1984, Shulman et al. 1999). In central Tanzania, chemoprophylaxis with a weekly dose of deltaprim to infants aged 8–48 weeks led to a 57% decrease in the incidence of severe anemia among 204 supplemented infants, as compared to the incidence in 207 infants receiving a placebo. This benefit against severe anemia was concomitant with a 60% decrease in the incidence of symptomatic malaria episodes in the treatment group (Menendez et al. 1997). In the same study, another group of 208 infants aged 8–24 weeks received a daily dose of iron, without antimalarial drugs, which reduced the incidence of severe anemia by 29% compared to the placebo group; thus, in this population, malaria appeared to be more important than iron deficiency as a cause of severe anemia in infants.

Table 3. Mechanisms leading to anemia in malaria:

- destruction of red blood cells (RBCs) by parasites
- phagocytosis of infected RBCs
- phagocytosis of uninfected RBCs
- impaired bone-marrow function
  - tumor necrosis factor (TNF) impairs erythropoietin output
  - reduced interleukin-10 response to TNF- hypersplenism
- other infections (↑ by malaria)
- intravascular hemolysis and hemoglobin uria

Several considerations affect the interpretation of epidemiological and interventional studies of the kind described above, in evaluating malaria control as a means of reducing anemia in populations. These considerations include:

1) The diversity of the problem—findings in one community may not be applicable everywhere or at all times because:
   - populations differ in their genetic constitutions, with differing prevalences of genes affecting the incidence of anemia and possibly also susceptibility to malaria
   - the intensity and seasonality of malaria affect the pattern of disease, and these characteristics of malaria transmission differ not only geographically but also from one year to another.

- severe anemia has a maximal incidence in infants and toddlers, while malarial coma appears to have a peak incidence in slightly older children. Some studies have suggested that the relative incidence of these two serious complications of malaria varies with transmission intensity (Snow et al. 1997).
- populations also differ in the prevalence and distribution of other factors that may affect the pattern of anemia, such as access to health services, prevalence of non-malarial parasitic and other microbial diseases (including HIV and related infections).
- *P falciparum* differs geographically and over time in its pattern of resistance to available antimalarial drugs.

2) Possible differences in etiology and control between mild/moderate and severe anemia:
   - some studies of interventions directed against malaria provide data on the effects on mean hemoglobin or pcv values; others report the incidence of new episodes of anemia or severe anemia (Hb<5g/dl). More studies are needed to identify the pathogenetic mechanisms of different degrees of anemia to determine whether severe anemia has a distinctive etiology and to target interventions (and assess outcomes) accordingly.

3) Antimalarial interventions in the context of other interventions against anemia:
   - some studies have shown an increase in malaria risk when iron deficiency is treated with iron (Oppenheimer et al. 1984). However, there was no adverse effect of iron therapy on malaria in pregnant women in a study in The Gambia (Menendez et al. 1994) and no adverse effect of iron on the incidence of malaria in Tanzanian infants (Menendez et al. 1997) or on the efficacy of treatment for malaria in Gambian children (Boele van Hensbroek et al. 1995).

4) Efficacy versus effectiveness:
   - this distinction applies to all intervention studies. For antimalarial interventions it is particularly important because of the association of malaria with poverty and the difficulty of sustaining programs with even modest requirements in finance, personnel, and administration. After the impressive efficacy of a trial of bed nets in The Gambia, one benefit of which was an improvement in mean Hb concentrations in children, a national bed net program was introduced into approximately half of the country's villages. Effectiveness was then evaluated by comparing villages with and without nets. Whereas in the trial in the Gambia bed nets were associated with a 60% reduction in all-cause child mortality, the figure was 25% (p=0.04) in the effectiveness study, with a non-significantly higher mean pcv in children in the bed net group (difference between groups was 0.49%). Thus, the intervention as a national program was effective against mortality, but the cost of the program was too high for the country to afford, and when cost-recovery from the population was attempted, bed net usage declined steeply and child mortality returned to pre-intervention levels.
   - chemoprophylaxis against malaria has been abandoned in most countries as a feasible intervention in children, because of the difficulty of delivering such a measure adequately. It remains a valuable intervention in pregnancy, although it has been replaced by intermittent presumptive treatment (IPT) with antimalarial drugs in many countries. The value of an IPT approach in children is being assessed in current trials.

5) Short-term versus long-term benefits:
   - even if an intervention against malaria can be sustained, there are concerns that the short-term benefit (e.g., against anemia) may be offset by longer-term disadvantages. In the study in Tanzania (Menendez et al. 1997) in which infants were given antimalarial chemoprophylaxis up to the age of 48 weeks, the reduction of malaria episodes and anemia during infancy was followed by an increased risk of both malaria and anemia in the second year of life. The possibility has been recognized that interventions such as chemoprophylaxis and bed nets may impair the acquisition of immunity and thus merely defer malarial morbidity to an age when it may be more severe. It is therefore important, but costly and difficult, to monitor the effects of malaria–including anemia and severe anemia–over the long term in countries with active malaria control programs (Lengeler & Snow 1996).

In conclusion, it is clear that malaria is an important cause of anemia and severe anemia. In some countries, it is the most important cause, especially in infants and young children. Malaria makes a significant contribution to anemia in pregnancy in many areas. Interventions against malaria, whether effective drug treatment or preventive measures, are highly beneficial to individuals and can have a significant impact on anemia at the population level. However, most antimalarial interventions are difficult to sustain for operational and financial reasons, and even if sustained, require long-term monitoring if their continuing effectiveness is to be known. Interventions must be suited to local situations, because of the diversity of people, parasites, and malaria transmission patterns. Reductions in both anemia and severe anemia are important potential gains from effective antimalarial interventions.

Discussion

Questions from the audience addressed additional factors that may be important for controlling anemia. Dr. Molyneux agreed that vitamin A and zinc might help. He did not support shifting the emphasis from malaria control to anemia control because malaria has many other devastating consequences beyond anemia.

Dr. Lozoff questioned the timing of the iron supplementation used in the Tanzanian study. Iron supplementation was given only in the first six months of life, yet it is the second six months that is the critical risk period for nutritional iron deficiency.

According to Helen Keller International, bed nets have been shown to be beneficial in Cambodia as well. Their data showed a reduction in malaria prevalence among children in three provinces where bed nets were used (25% prevalence of malaria) compared with children without bed nets (45% prevalence of malaria).

Helminths

Dr. Lesley Drake, Partnership For Child Development, Imperial College School of Medicine, London, United Kingdom, discussed deworming as a strategy to combat anemia. Worms are a significant cause of anemia and worm control programs contribute to anemia reduction. Worm infections are the most ubiquitous of all chronic human infections. Several worm species cause the most common infectious diseases in the world today. The most common species of intestinal worms are the roundworm (Ascaris), the whipworm (Trichuris) and the hookworms (Ancylostoma and Necator). Some or all of these worms cause blood loss from the gut.

The other species that can cause mechanical blood loss are the blood flukes (Schistosoma species). The adults inhabit the mesenteric vessels around the bladder or intestine, in pairs, permanently in copula. These species cause blood loss primarily by the migration of the eggs as they rupture blood vessels and invade either the bladder or the intestine on their quest to reach the outside world.

Worldwide in 1997, there were estimated to be over 1200, 1000, and 800 million cases of hookworm, Ascaris, and Trichuris respectively. For Schistosoma species, there were around 200 million cases.

Important and depressing to note is that the prevalence of these infections has hardly changed over the past 50 years. The absolute numbers of cases has increased due to the increase in the absolute number of people now living on our planet.

These infections are widely distributed, but it is apparent that where worm infections are prevalent, anemia is also likely to be prevalent. Worms thrive in communities that are in need of improved housing, sanitation, clean water, education, and increased personal earning. That is, worm-related infections are a consequence of poverty. Poor communities are also at risk for anemia.

School-aged children (a risk group for anemia) are most at risk from disease morbidity. Infection first occurs early in life, rises to a maximum in childhood and settles to a stable asymptote in the adult population. However, if looked at according to the age-intensity (or worm burden), the profile is convex in shape. In other words, school-aged children have the most intense infections. Because morbidity is directly related to the intensity of infection, it follows that this age group is particularly susceptible. A similar picture is noted for Schistosoma age-infection patterns.

The main mechanism by which worm infections can contribute to the anemic state is direct blood loss, although other mechanisms may contribute. Whipworms can cause blood loss as a result of dysentery and mucosal damage. Although it is likely that this is only significant in severe infections. An association has been shown between anemia and the roundworm, although how this is facilitated is unclear – possibly through malabsorption or inappetency.

The most significant infection causing blood loss is hookworm infection, with the magnitude of blood loss being directly related to the number of adult worms present. The worm uses sharp blades or teeth in its buccal cavity to cut into tissues. The worms' powerful pharynx then sucks up blood and tissue fluids and contributes to blood loss by feeding. The worm moves to a different site several times a day and the damaged tissue continues bleeding. This is further exacerbated by the secretion of an anticoagulant by the hookworm. Also, hookworms live in the duodenum, where most iron absorption occurs and it is hypothesized that worms may also interfere with the uptake of iron. Moderate to heavy burdens of hookworm infection may also impair appetite.

Data show a relationship between infection intensity and hemoglobin levels: as infection intensity increases (as indicated by an increase in egg output, i.e., eggs/gram of feces), hemoglobin levels decrease (Brooker et al. 1999, Lwambo et al. 1992, Beasley et al. 1999).

Estimates of blood loss indicate that a single Ancylostoma worm is responsible for the loss of 0.15ml/day of blood. This is more than for the other main hookworm species, Necator, with an estimated 0.03ml/day/worm. Thus, 25 Ancylostoma worms or 110 Necator worms would cause a loss of about 5ml blood a day, containing 1.85mg of iron. Note that these are not particularly heavy infections (Pawlowski et al. 1991). It has been estimated that an infection with 25 Necator worms resulting in an iron loss of 0.347mg/day would completely deplete a woman's iron stores in 2 years–irrespective of other insults on her iron status (Pawlowski et al. 1991).

Schistosoma infections can also lead to blood loss. S. haematobium eggs reach the external environment by penetrating into the bladder and subsequently being released with host urine. Female S. haematobium release their eggs into the smallest blood vessels surrounding the bladder that they can reach, from where the eggs penetrate the bladder wall with help of sharp spines on the eggs. S. mansoni eggs are released via the intestine,

reaching the gut lumen in a similar manner. This activity leads to tissue damage and blood loss.

Preschool- and school-aged children and pregnant women are most at risk for hookworm-attributable anemia. Attributable fraction analyses indicate that for preschool-aged children, anemia in 14% of infected children and in 28% of heavily infected children was attributable to hookworm infection (Brooker et al. 1999). Among school-aged children, anemia in 25% of infected children and in 73% of heavily infected children was attributable to hookworm infection (Brooker et al. 1999, Stoltzfus et al. 1997). A study estimating the proportion of anemia attributable to hookworm infection in pregnant women in Nepal estimated that 29% of all iron deficiency anemia and 41% of moderate to severe anemia was attributable to hookworm infection (Dreyfuss et al, 1996).

At the individual level there are significant benefits to be gained in controlling anemia through deworming (e.g., anthelminthic treatment during pregnancy). Effects of controlling anemia have also been shown at the population level. For example, after 3 rounds of treatment over 15 months, significant increases of 7.2g/L Hb and 6.8 μg/L serum ferritin were observed in an intervention group. Perhaps more importantly, at an operationally realistic scale, significant increases in hemoglobin can also be made by simple mass deworming (Beasley et al. 1999, Hall et al. 2001).

Deworming is practical and mass targeting of school children is a particularly practical and cost-effective approach. The existing educational infrastructure—including teachers—can be used for delivery. The single-dose drugs are safe and can be administered by appropriately trained teachers as well as public health workers. Also, by delivering through schools, delivery costs can be kept to a minimum so most of the cost is the drug itself. For example, in Tanzania in 1997, it cost less than US$0.80 per child to deliver praziquantel and less than US$0.20 per child for albendazole. These drugs are now even cheaper and alternative, free drugs are also available from the private sector and humanitarian foundations.

In terms of disability adjusted life years, deworming, as a type of intervention is comparable to other mechanisms for anemia reduction such as fortification and supplementation. The 1993 World Development Report recommended that funding be made available for mass treatment programs for large-scale (global) control of helminths. These programs are increasingly being implemented. A major initiative is FRESH (Focusing Resources on Effective School Health) Start, a multi-agency partnership among the World Bank, WHO, UNICEF, and UNESCO. This program outlines the basic framework for an effective school health program and school-based delivery of these interventions and highlights how effective and cost-effective this strategy is. There are now more than 20 countries in Africa adopting the FRESH Start framework.

Anemia and worm infections are exceptionally common and where these 2 conditions occur together, anthelmintic mass treatment programs offer a highly cost-effective strategy that can contribute to efforts to reduce iron deficiency and anemia.

Discussion

In response to questions from the audience, Dr. Drake said that deworming programs administered through schools are sustainable and cost effective. The cost of a single dose of albendazole is less than US$0.05. Mebendazole is less expensive and less efficacious against all helminths. The drugs are the most expensive component of a successful deworming program. Delivery of deworming drugs must be accompanied by health education and sanitation if the program is to succeed. Use of night soil is a major cause of infection in communities even where safe drinking water is available. The real issue is sanitation not just safe water.

WHAT TO DO ABOUT IRON DEFICIENCY

Iron Supplementation: Comparison of daily and weekly iron supplementation

Background

Dr. George Beaton presented a paper prepared by Dr. George McCabe and himself. The paper addressed the controversy of daily or weekly iron supplementation use in field programs. It was based on the full analysis of experience to date published by Beaton and McCabe.[2] A WHO/INACG/MI consultation (Washington D.C., 1999) addressed the program implications of the meta-analysis and will be published separately. The wording of the present paper reflects the editorial input of the first drafting of the WHO/INACG/MI consultation report.

Anemia is accepted as a major public health problem in almost all non-industrialized countries. Iron deficiency has commonly been cited as the main cause of anemia, but in many situations it coexists with parasitic diseases and perhaps also contributing micronutrient deficiencies (Beaton 2001).

Direct iron supplementation continues to be the most common operational approach to control anemia; attempts to introduce iron fortification or diet modification are underway in some settings. In general, progress in the control of iron deficiency anemia in the field has been disappointing and progress in reducing the magnitude of the problem remains limited.

In the 1990's, two research groups (Wright and Southon 1990, Viteri et al. 1995) independently reported that iron absorption in iron-depleted rats was similar or greater when iron was administered intermittently as compared to daily administration. It was hypothesized that daily doses of iron saturated the absorption pathways in gut mucosal cells but absorption was enhanced when dosing was phased with mucosal cell turnover. Two subsequent absorption studies in humans failed to replicate the findings (Cook and Reddy 1995, Olivares et al. 1999).

Nevertheless, the initial reports stimulated hope that a new and possibly more effective approach to the field problem of iron deficiency anemia was at hand. Weekly supplementation was seen as having many potential advantages, compared to daily supplementation, if weekly supplementation were found to be effective. Suggested advantages included reduced side effects and improved adherence, and lower purchase and distribution costs.

The first human trial comparing daily and weekly dosing was conducted with Chinese children resulting in very encouraging findings (Liu et al. 1995a). A second study, also conducted in China, reported encouraging findings for pregnant women (Liu et al. 1995b). Following these reports, many studies were initiated throughout the world to test the hypothesis that weekly iron administration was as efficacious as, or more efficacious than, daily administration. In 1993, UNU, WHO, and UNICEF developed a master protocol for these studies (WHO/UNICEF/UNU 1993). By 1997, considerable data had accumulated and results were being widely reported, although, relatively few of the individual studies had been published in the open press. Against this background, Beaton and McCabe were invited by the Canadian International Development Agency and the Micronutrient Initiative to collect and analyze the findings to date.[2] Research conducted up to the point when Beaton and McCabe started their work was focused on the question of biological efficacy. There was little information concerning effectiveness or efficiency/cost-effectiveness of weekly

[2] Note that since few of the studies had been published, the review involved the active cooperation and collaboration of the original investigators. Beaton and McCabe are deeply grateful for the cooperation of so many who shared with them their actual data as well as their own summary analyses. Others were able to provide only summary analyses; a few of the early studies also appeared in print as abstracts or full papers and provided summary analyses.

versus daily iron supplementation programs. Therefore, Beaton and McCabe could not address these extremely important issues.

The Beaton and McCabe Analysis

A total of 21 completed efficacy trials were identified for the study as well as an additional 2 trials in progress for which investigators were prepared to release preliminary results. The studies were identified by contacting investigators, key informants, canvassing national and international agencies, and conducting conventional literature searches. For 14 of the 23 trials, investigators released the actual data for the Beaton and McCabe secondary analyses. For the other 9, only summary statistics were available from the investigators or from published papers, abstracts, and meeting reports. Studies were included in the analyses if the study design was judged adequate and information available provided minimally required data for the particular analysis. Although highly desirable, the inclusion of a placebo-controlled group was not required, and in fact, none of the pregnancy studies and few of the studies with preschool-aged children included such a control.

Where full data sets were available de novo analyses of hemoglobin and serum ferritin data were conducted. Three trial outcomes were reported. First, the treatments were compared using the post-treatment hemoglobin values adjusted for baseline values. Second, a parallel analysis for serum ferritin (fewer studies) was performed. Third, the relative risk of being anemic at the end of the treatment intervention was analyzed. This last analysis included the greatest number of trials since only summary statistics from the studies were needed. In generating summary estimates of the comparison between daily and weekly supplementation, several approaches to weighting individual studies were examined and reported. Confidence intervals for the summary estimates were derived for both fixed effect and random effect models. All analyses were subjected to sensitivity testing and other checks of assumptions in the models.

Detailed results showing each study are available in the full report .[2,3] For hemoglobin change as outcome, 11 of the 13 studies found greater hemoglobin increase in the daily-supplemented group than in the weekly-supplemented group and the summary estimate of the difference in effect was +2.34 g/L (95% confidence limits 0.13 to 4.55 in favor of daily supplementation). For serum ferritin as outcome, all of the 7 studies found greater improvement in ferritin in the daily-supplemented group, and the summary estimate was +11.24 μg /L (95% confidence interval 8.31 to 16.29). For post-treatment anemia, 14 of the 19 studies found a greater risk of anemia in the weekly-supplemented group. The summary relative risk of being anemic was 1.34 (95% confidence limits 1.20 to 1.49).

The most notable finding in these analyses is the high degree of consistency. Whether one looks at the impact on group mean hemoglobin or serum ferritin, or at the relative risk of being anemic after the intervention, it is clear that daily supplementation had a greater effect than weekly supplementation. Although the greater improvement in mean hemoglobin associated with daily supplementation was small (2 g/L), the relative risk of anemia in the weekly-supplemented groups (a 34 % higher risk) was judged to be biologically significant, especially in public health terms.

The data were further explored to see whether certain defined characteristics of the population were predictive of the relative success of weekly supplementation compared to daily supplementation. The relative efficacy was remarkably consistent across

[3] The summary estimates now presented differ slightly from those in the full report since now only data from completed studies are included. Two studies (Korea and Mexico), which were still in progress, have been omitted from the present analyses since the final data are not available. The impact of these omissions is very small. In the original report, ferritin data were presented only in log form; they are now converted back to linear units.

age subgroups. Baseline anemia prevalence was a predictor of final prevalence but not of the relative benefit of daily versus weekly supplementation. Within the three studies that measured hemoglobin at more than one post-intervention time point, longer duration of the intervention yielded a greater hemoglobin response. It might be hypothesized that with continuing supplementation, the effects of daily and weekly administration would merge at some sort of physiological plateau. However, across projects, duration of intervention did not explain the difference in the relative risk of anemia associated with daily or weekly supplementation. In other words, there was no evidence that weekly supplementation performed better relative to daily supplementation in trials with longer supplementation periods in the time range included in the studies examined (pregnancy studies, 10–19 weeks; school children and adolescents, 8 –24 weeks; preschool children, 8–18 weeks).

Compliance with iron supplementation was evaluated variously in the different studies, and this could not be used quantitatively in the analyses of collective experience. Subjective categorization of studies into five categories of "degree of control" of the study population suggested that situations likely to provide higher compliance resulted in lower post-treatment rates of anemia. This control category did not alter the relative risk associated with weekly supplementation compared to daily supplementation. But, because the final anemia rates were lower in the more controlled settings, the absolute difference between anemia rates in the two groups became small. The converse was also true; where final prevalence remained high, the absolute difference between weekly and daily supplementation was high and potentially a matter of public health concern (Beaton 2001).

Again, because of differences in the ways in which data pertaining to possible side effects were collected and presented across individual projects, it was not possible to conduct an analysis of collective experience.

Separate comparisons of daily and weekly supplementation with placebo control (for those studies that included a randomized placebo group) showed that both daily and weekly dosing had statistically significant positive effects on hemoglobin and risk of anemia, with a greater effect for daily administration. Both supplementation regimens were efficacious, that is, significantly better than no supplementation.

Main Conclusions

- Both daily and weekly iron administration can reduce iron deficiency anemia; both treatments were *efficacious*.
- Daily administration was more efficacious than weekly to improve hemoglobin, reduce anemia, and increase iron stores. The overall picture, however, was that neither appeared to be very *effective*.
- There was no evidence to conclude that intermittent iron administration carried any physiological advantage in terms of control of iron deficiency anemia. The results of the present analyses fail to support the hypothesis that, for biological reasons, weekly supplementation would be more efficacious than daily supplementation.
- The relative efficacy of daily compared to weekly supplementation did not differ by class of subject (pregnant women, school-aged children and adolescents, and preschool-aged children), or any other population characteristic that was measured.
- Many studies had a high residual prevalence of anemia after the interventions, even with daily supplementation. In this situation the absolute difference between daily and weekly supplementation was greater.

Judged Implications

Based upon their judgment and review of the general literature rather than on the direct analyses, the authors also suggested that:

- While both daily and weekly supplementation are *efficacious*, one is forced to conclude that neither daily nor weekly supplementation was very *effective* in controlling the problem of anemia as currently defined, even in these research settings. This should be the matter of major public health concern, outweighing the differences in opinion about whether daily or weekly supplementation would be more appropriate in one setting or another.
- It would be imprudent to advocate the use of weekly iron supplementation in pregnancy.
- Daily supplementation is more likely to be effective except when supervision is feasible with weekly regimens and not feasible with daily regimes. One situation in which weekly iron supplementation (for all but pregnant women) *might* have specific advantage is in school-based supplementation and perhaps selected institutionalized situations where supervision/ reinforcement is feasible for weekly but not daily supplementation.
- It seems likely that the most important factors to establish effective operational programs for the control of anemia will be the use of integrated strategies to address all causes of anemia and attention to the manner in which programs are managed and compliance is reinforced.

Multi-Micronutrient Supplementation

Dr. Werner Schultink, UNICEF, New York, USA, stated that at the 1990 World Summit for Children, heads of state and government agreed to the 2000 goal of reducing iron deficiency anemia in women by one third of 1990 levels. However, little progress has been made in achieving this. Iron/folate supplements have had little impact in reducing the prevalence of anemia. Reasons for this failure include inadequate delivery of supplements, poor clinic attendance during pregnancy, poor compliance, and poor communications strategies. Other important factors are the diversity of causes of anemia, notably deficiencies of vitamin A, zinc, vitamin B12, or folate. There is also a noticeable lack of political will to attack the anemia problem.

Programmatically it would be more efficient and more effective to combine micronutrients as opposed to delivering them individually. As the intake of multiple micronutrient supplements has been part of the daily routine for many adults and children in the industrialized world for the past decade, so should the same opportunities be available for people in the developing world. While recognizing that micronutrients should ideally be obtained by diversifying diets and increasing intakes of nutrient rich foods through fortification, the reality of economic constraints, seasonal harvest, limited production, and poor delivery infrastructure in developing countries make it difficult. Also, the nutrients available in a diversified diet would still not be sufficient for specific target groups such as pregnant women.

UNICEF has sponsored a number of workshops to determine the composition of the multiple micronutrient supplements. The concentration of the nutrients is based on the US Recommended Dietary Allowance and each tablet currently costs US$ 0.08. With donors and foundation support, multiple micronutrient trials are being done on infants and young children as well as pregnant women. The preschool trials are underway in Indonesia, Vietnam, South Africa, and Peru, and the anticipated outcome indicators include improved growth and reduced morbidity. Trials on supplementation in pregnancy are being conducted or are about to start in Indonesia, Bangladesh, Tanzania, Niger, Nepal, Vietnam, China, Madagascar, Mozambique, Philippines, India, and Pakistan. The anticipated outcomes include improved maternal micronutrient status and decreased prevalence of low birth weight infants. The prenatal studies are being conducted in the framework of low birth weight reduction

programs, in which there is an education component emphasizing the need for better support of pregnant women and growth monitoring during pregnancy. Depending on the country, control of malaria (especially in primigravidae where appropriate), food supplementation, deworming, and the prevention of teenage pregnancies are also included in the interventions. Once the study results are available, a review will be held with WHO to establish recommendations for universal multimicronutrient supplementation for children, pregnant, and lactating women.

Discussion

There was clearly support in the INACG audience for a stated goal of the 2001 World Summit for Children to be a reduction of anemia and iron deficiency worldwide. Dr. Schultink supported the anemia goal because it is easily measured and there are a range of interventions that can be cost-effectively implemented, i.e., micronutrient supplements, bed nets, and deworming. He was doubtful that complete elimination is possible, as this has not been achieved in well-developed countries.

Dr. Beaton reiterated his view that it would clearly be disadvantageous for women to enter pregnancy with a significant iron deficit. Conversely, too much attention on building iron stores before pregnancy, without assuring an adequate iron supply during pregnancy, might be an unfortunate error. The body is exquisitely equipped to adjust iron absorption in response to body need and tissue reserves, even in pregnancy (Beaton, 2000). Increasing stores before pregnancy might reduce absorption in early stage of pregnancy, if so the assumed benefit of the pre-pregnancy store would be greatly diminished. The hypothesis of beneficial effects of pre-pregnancy iron stores greater than those associated with avoidance of anemia, remains untested. While control of anemia in women of reproductive age can be argued as important, there may not be a strong foundation for arguing that storage iron should be increased before pregnancy. Again, it is a matter for carefully defining realistic and functionally important objectives.

Dr. Keith West, Johns Hopkins University, said that the efficacy of prenatal multiple micronutrient supplements is unknown with respect to birth weight, intra-uterine growth, and infant mortality. He urged nutrition program decision-makers to wait for the results of the ongoing efficacy trials before embarking on less sensitive effectiveness trials and pilot programs.

Based on an efficacy trial with at multiple micronutrient supplement drink in Tanzania (Ash et al. in press), Dr. Deborah Ash, Harvard University, urged attention to the social acceptability of such supplements.

The appearance of the supplement must be acceptable and its purpose clearly understood. Specific issues will vary from country to country. For example, the presence of porcine gelatin in some supplements is offensive to specific religious groups. Dr. Schultink explained that the multiple micronutrient supplements being used in Indonesia were manufactured in country without porcine gelatin and this could be done elsewhere, but the cost would increase.

Dr. Tommaso Cavalli-Sforza, WHO Regional Office for the Western Pacific, voiced support for supervised weekly iron/folate supplements for school children and women of reproductive age. In a study in Vietnam, school children are given iron/folate tablets along with nutrition education messages. Supplements are also available to women of reproductive age.

As a result of appropriate education, 60-90% of reproductive age women in the study regularly purchased iron supplements at work through the Women's Union (abstract # 24). Up to 100% of pregnant women took iron supplements during the last four months of pregnancy. A revolving fund has been created by the Women's Union to purchase more supplements.

In the Philippines, supplements may be purchased through pharmacies and their use is much lower. Dr. Cavalli-Sforza suggested that the approach of buying a cheap community supply of iron in Vietnam might be applicable to multinutrients as well.

Food Fortification

Dr. Richard Hurrell, Institute of Food Science, Swiss Federal Institute of Technology, Zurich, Switzerland, discussed an overview of food fortification as a strategy to combat iron deficiency and stressed that fortification with iron has been proven efficacious in several settings, despite the general difficulty of adding iron to food.

Iron is the most difficult mineral to add to foods and to ensure adequate absorption (Hurrell 1999). This is because the more bioavailable iron compounds, such as ferrous sulfate and ferrous fumarate, often cause unacceptable color and flavor changes to the food vehicle. This has led to the widespread use of compounds such as elemental iron, which are organoleptically inert but poorly absorbed. In addition, high phytic acid intake from the fortified food, or from other foods consumed with fortified foods, further limits iron absorption. For this reason, and also partly because of poorly designed studies, it has never been clearly demonstrated that iron fortified wheat flour, maize flour, or salt improve the iron status of targeted populations. The iron fortified foods that have been demonstrated to improve iron status are infant formulas and infant cereals where ascorbic acid has been added to enhance iron absorption, and soy sauce, fish sauce, curry powder, and sugar, all foods fortified with sodium iron ethylenediaminetetraacetic acid (EDTA), an iron compound of relatively high bioavailability which also counteracts the inhibition of phytate (International Nutritional Anemia Consultative Group (INACG) 1993).

Cereal products are often fortified with elemental iron powders, which are not a single entity. They can be manufactured by 5 different processes (electrolytic, H-reduced, H-reduced (atomized), CO-reduced, carbonyl) giving powders of different particle characteristics, which in turn govern the dissolution of the powder in the gastric juice and its relative bioavailability. A recent workshop reviewed published data on elemental iron involving rat and human bioavailability studies and efficacy studies (Hurrell et al. submitted). It was concluded that only electrolytic iron powders had been demonstrated as useful iron fortificants. The usefulness of reduced iron powders was unclear, and although most commercial powders appeared to be relatively poorly absorbed, it was noted that it could be possible for the manufacturers to make powders with an equivalent bioavailability to ferrous sulfate (Hurrell et al. submitted).

Encapsulated ferrous sulfate or fumarate can also be used to fortify cereal flours or salt without sensory changes and these iron fortificants have not been fully exploited. Capsules based on hydrogenated oils seem most suitable and bioavailability of these capsules in animal studies remains unchanged (Hurrell 1999). However, even with highly bioavailable compounds, iron absorption will be low in the presence of phytate. This can be overcome by the addition of ascorbic acid (Forbes et al. 1989) or sodium EDTA (Hurrell et al. 2000) together with the iron compound, by adding sodium iron EDTA (Hurrell et al. 2000), or by phytate degradation (Hallberg et al. 1987).

In order to promote a successful food fortification program by optimizing iron absorption, the following recommendations can be made:

- Where possible use ferrous sulfate and ferrous fumarate, if necessary in encapsulated form.
- Use only electrolytic iron powders for cereal fortification until manufacturers have improved and standardized reduced iron powders.
- Use ascorbic acid as an enhancer of iron absorption.

- With fortified foods high in phytate, and foods consumed with high phytate diets, use NaFeEDTA (or Na_2EDTA as an absorption enhancer).
- Degrade phytic acid in complementary foods for food aid programs.

Discussion

Dr. Anna Verster, WHO Eastern Mediterrean Regional Office, reported that two Middle Eastern countries were already fortifying wheat flour with iron and folate. Six other countries are planning to start such national programs very soon. Three others are waiting to complete trials and two have decided that all imported flour (90% of consumption) must be fortified. A regional standard has been developed – 30 ppm iron from ferrous sulfate or 60 ppm from elemental (electrolytic) iron. Some countries prefer elemental iron because of improved shelf life. In other countries the flour-to-bread turnover is high so ferrous sulfate can be used. The levels of fortification for elemental iron are double that of iron from ferrous sulfate to compensate for the lower bio-availability of elemental iron. In addition, countries are advised to use, wherever possible, electrolytic iron of high quality and fine mesh-size.

Dr. Eva Hertrampf, University of Chile, mentioned that ferrous sulfate works well with wheat flour in Chile. The shelf life is 4-6 weeks.

In response to a question regarding addition of zinc along with iron, Dr. Hurrell stated that zinc fortification is easier than iron. Zinc absorption is also inhibited by phytic acid and enhanced by EDTA. Several studies have shown interactions between zinc and iron absorption, but when added to foods (in amounts commonly used in food fortification programs), neither inhibits the absorption of the other.

Dr. Hurrell responded to a question regarding the potential for double fortification of salt with iron and iodine (abstract # 37) saying that salt is difficult to fortify because of color changes and losses of iodine. The system developed by the Micronutrient Initiative uses ferrous fumarate and encapsulated iodide. The National Institute of Nutrition in India developed a system using sodium hexametaphosphate and ferrous sulfate. However, further development is needed to overcome the technical problems involved in double fortification of salt.

Recent Experience With Food Fortification

Four ongoing food fortification efforts were described at the INACG symposium. Three of these were research projects and the fourth a national program.

Dr. Penelope Nestel, USAID's Micronutrient Global Leadership Project, Washington DC, USA, presented preliminary results of a two-year, double blind, wheat flour fortification effectiveness trial in Sri Lanka. An earlier study (Piyasena et al. 1996) had shown that 85% of the population purchased wheat flour. The average consumption was 70g/person/day in rural areas and 165g/person/day on the tea growing estates. Urban consumption fell between these two levels. Preschool children consumed 140g/person/day from the same diets as the adults. Based on the above, the flour was fortified with 66 ppm iron.

Three randomized study groups were drawn from six highland tea estates to receive electrolytic iron, reduced (atomized) iron, or no added iron (the control group). The study groups were children, 9-71 months of age; children, 6-11 years of age; and women of childbearing age. Hemoglobin, zinc protoporphyrin, and ferritin were measured, but only hemoglobin values were reported.

The analysis was disagregated by fortification type. At baseline, the anemia prevalence was half of the expected level based on previous surveys and there were no overt differences among the treatment groups after two years of intervention.

In view of the discrepancy in venous hemoglobin levels in this study versus the national survey that was based on capillary

blood samples, Dr. Abe Parvanta, U.S. Centers for Disease Control and Prevention, noted that there is a pressing need to develop guidelines to standardize sampling procedures for finger-prick capillary blood samples for hemoglobin analysis to improve the understanding of the true prevalence of anemia where instruments such as the HemoCue are used. In his opinion, the HemoCue is an excellent instrument, but appropriate and rigorous training for the operators is essential.

It was also pointed out that the improvement in the control group anemia status in the Sri Lanka study could have resulted from improved diets, such as eating more poultry. More attention should be given to dietary modification approaches for anemia control.

For the second food fortification effort, Dr. Pham Van Thuy, National Institute of Nutrition, Hanoi, Vietnam, reported results from a double blind efficacy study of fish sauce fortified with sodium iron EDTA (abstract #35). More than 80% of adults in Vietnam consume 10-15 ml fish sauce per day. The study included two groups of non-pregnant, anemic (hemoglobin <120 g/L) female factory workers of childbearing age. Approximately half of the women were iron deficient at baseline.

Each individual ate a rice test meal under supervision six days a week for six months. The meal contained 10 ml fish sauce that was unfortified (control group, n=68 women) or fortified with sodium iron EDTA (n=62 women) to supply 10 mg iron/person/day. Hemoglobin, ferritin, and transferrin receptor levels were measured at baseline and after three and six months of intervention.

After six months of the study, the prevalence of anemia had decreased by 34% in the fortified group and 10% in the control group. There was a significant rise in the serum ferritin levels and decrease in circulating transferrin receptor concentrations in the fortified group, with no significant change in the control group. The prevalence of low plasma ferritin (<12 μg/L) and elevated transferrin receptor (>8.5 mg/L) decreased significantly after 6 months to 16% and 29% in the fortified group, respectively. In the control group, the corresponding values were 49% and 51%. Thus, there was a significant improvement in the iron status of the group receiving iron fortified fish sauce compared to the control group. Dr. Thuy concluded that fortification of fish sauce with sodium iron EDTA might be an effective strategy for controlling iron deficiency anemia among women in Vietnam.

Dr. Eva Hertrampf, University of Chile, Santiago, Chile, reviewed the Chilean experience of providing iron-fortified milk to mothers and young children. The Chilean Ministry of Health supplies 2 kg full-fat powdered milk free of charge to 70% of infants between birth and 18 months of age in this national program. This milk has been fortified with iron (ferrous sulfate), vitamin C, zinc, and copper since 1999. Lactating women are instructed to drink the milk until their children are weaned and then to feed the milk to the children. The bioavailability of the iron is high: mean of 12% as measured with stable isotope technique in 9-13-month-old infants.

A random cohort of children, aged 12-18 months, was evaluated in June and July before the implementation of the fortification program and a second cohort in the same age range evaluated a year later. Hemoglobin, zinc protoporphyrin, and ferritin were measured. There was a significant shift to the right in the distribution curve for hemoglobin levels. Twenty-nine percent were anemic before the intervention and only 9% in the group evaluated a year later. The percentage of infants with high zinc protoporphyrin values decreased from 67% to 32%. There was no significant change in ferritin values. Dr. Hertrampf concluded that the delivery of iron and vitamin C-fortified powdered milk to infants is an effective strategy for controlling iron deficiency.

Finally, Dr. Stanley Zlotkin, Hospital for Sick Children, Toronto, reported on the use of "sprinkles" to deliver micronutrients to very young children (abstract #38). With "sprinkles," encapsulated iron can be added directly to infant food prepared at home. This is an innovative alternative to iron drops, which have a bad taste, stain teeth, and are difficult to accurately deliver. "Sprinkles" sachets are easy to transport, unlike the drops in glass bottles, and easy to manufacture. The cost for production in Dr. Zlotkin's laboratory was US$ 0.023 per sachet.

A study among mildly anemic Ghanian children, aged 6–18 months, fed either the iron-containing "sprinkles" or iron drops found that anemia was corrected (hemoglobin >100 g/L) in 58% of the children receiving "sprinkles" and 56% of those receiving drops. A no-treatment control was not included, as this was considered unethical because these children were mildly anemic. Children whose anemia was corrected in the first study were eligible to participate in a second study.

In the second study, children were randomized into four treatment groups: placebo, iron drops, "sprinkles," and "sprinkles" with vitamin A. Non-anemic hemoglobin levels were maintained for six months in 82% of the children. There were no significant differences among the groups. Dr. Zlotkin concluded that "sprinkles" worked as well as iron drops in correcting anemia in infants and were well accepted. Their use provided enough iron to maintain normal iron stores for at least six months.

Other micronutrients could be added to the "sprinkles" preparation, so that the contents of sachets could be tailored to meet specific micronutrient needs of a particular community. "Sprinkles" have no unacceptable organoleptic effects on the food to which they are added, but have an unpleasant taste if eaten without food. This should reduce the risk of accidental poisoning.

CONCLUDING REMARKS

Dr. Lena Davidsson gave the concluding remarks at the 2001 INACG symposium. Iron deficiency in its most severe form results in anemia—iron deficiency anemia (IDA)—and since anemia (hemoglobin below established cut-off levels) is relatively easy to diagnose, the prevalence of anemia has often been used as a proxy for IDA. Although this approach can be useful in settings where iron deficiency is the major cause of anemia, it is less valid in regions where the etiology of anemia is more complex. As discussed in this publication, malaria, helminth infection, and other infections causing inflammatory response are important factors contributing to the high prevalence of anemia in many developing countries. In addition, the prevalence of other nutritional deficiencies (vitamin B_{12}, folate, and vitamin A) as well as hemoglobinopathies and HIV infection need to be considered in many regions. Furthermore, a number of these infections and nutritional deficiencies can be expected to coexist in individuals, further complicating the accurate diagnosis of IDA. For example, recent data from Côte d'Ivoire (Staubli Asobayire et al. 2001) clearly demonstrate the limited usefulness of anemia as an indicator of IDA. In this study, a large proportion of anemia cases were IDA in young children (80%) while only 20% of anemia was due to iron deficiency in adult men. In addition, the complexity of the etiology of anemia was shown by the overlap between IDA and infection, in particular in young children.

Thus, there is an urgent need for more specific diagnostic tools to identify iron deficiency, in particular in populations with high prevalence of infections, as discussed by Dr. Cook at the 2001 INACG Symposium. The usefulness of the circulating transferrin receptor was demonstrated in the study in Côte d'Ivoire and, although further validation of the method is needed, this technique is very promising.

The specific difficulties in diagnosing iron deficiency and IDA in different regions are important considerations when collecting prevalence data as well as when monitoring the impact of strategies aimed at increasing iron intake. Simply monitoring changes in hemoglobin concentration in regions where the etiology of anemia is multifactorial will not be a useful approach to monitor the effect of interventions with iron fortified foods or iron supplements. The lack of "success stories" can probably be related to the limitations of the monitoring and evaluation process in many cases and highlights the need for careful consideration of status indicators and population groups included in the evaluation. For example, the impact of iron supplementation during pregnancy needs to be re-evaluated with special emphasis on the most "at risk" individuals, that is, women with moderate or severe anemia as suggested by Dr. Beaton.

Food fortification is often suggested as the best long-term approach to increase iron intake. However, in order to establish a successful food fortification program, a number of important factors need to be considered. The choice of the food vehicle will obviously depend on the overall approach. For example, the most frequently fortified foods include cereal flours to increase iron intake in the general population and infant foods for targeted food fortification programs. The choice of the iron compound should be based on bioavailability and stability in the product. Unfortunately, iron compounds with high bioavailability often provoke unacceptable fat oxidation and changes of color, taste, and odor during storage or food preparation. Consequently, less soluble and thus less bioavailable iron compounds are often used, for example elemental iron to fortify cereal flours.

The usefulness of the fortified food should be demonstrated by monitoring the impact on iron status, for example by reducing IDA in the study population, in well controlled "efficacy studies." Effectiveness of a food fortification program is more difficult to evaluate since changes in iron status are monitored in less controlled settings, in settings closer to the "real life situation." Due to the numerous difficulties and great expense involved in organizing large-scale effectiveness studies, this type of evaluation is rarely made. Alternatively, the possibility of evaluating effectiveness (including cost-benefit analysis) during implementation of efficacious food fortification strategies should be explored.

As stressed by Dr. Hurrell, it is important to note that iron fortification of staple foods such as cereal flours has not been demonstrated to be efficacious. However, this approach, in particular iron fortification of wheat flour, has been implemented in many countries and is often suggested as a useful strategy to increase dietary iron in the general population. Alternatively, iron fortification of frequently consumed condiments can be used to reach a large segment of the population. The usefulness of condiments as vehicles for food fortification has been reported and was recently evaluated in Vietnam. The results presented by Dr. Thuy clearly demonstrated that iron fortification of a widely consumed condiment, fish sauce, using a water soluble iron compound with high bioavailability (NaFeEDTA), was efficacious in reducing the prevalence of IDA in women. This strategy would thus seem a useful approach, in particular in countries where rice is the major staple food since rice is difficult to fortify with iron.

Possibilities to improve iron bioavailability from fortified foods also need to be explored, for example by degrading phytic acid–a potent inhibitor of iron absorption present in cereals and legumes–by enzymatic treatment. Degradation of phytic acid could be particularly useful for cereal based foods such as complementary foods for infants or foods distributed via food aid programs. However, large proportions of vulnerable population groups in many countries do not have access to industrially produced foods and food fortification is therefore not an option. Novel approaches need to be further explored, for example the use of "sprinkles" to fortify home made complementary foods, as discussed by Dr. Zlotkin.

Dietary diversification as a strategy to improve iron status was not discussed during this symposium due to time constraints, but the potential to increase iron intake or improve iron bioavailability by simple dietary modifications needs to be carefully evaluated as suggested by Dr. Tagwireyi in her remarks. For example, data presented in a poster at this meeting demonstrated that human milk could be a major source of ascorbic acid in the diet of infants and young African children, potentially useful to improve iron bioavailability from complementary foods (abstract #29).

In conclusion, Dr. Tagwireyi's keynote lecture focused on the frequently asked question, "Why has so little progress been made to reduce the prevalence of iron deficiency and IDA?" Obviously, there are no simple answers to this query but, as pointed out by Dr. Beaton, there is a need to re-evaluate the impact of existing programs and to focus on "at risk" individuals. In particular, the benefit of iron supplementation during pregnancy should be evaluated in women with moderate or severe anemia since the risk of maternal mortality is related to the severity of the anemia. As highlighted by Dr. Lozoff, more information is needed on the importance of iron deficiency and IDA in early life, in particular on the functional outcome of deficiency at different stages during early development. We now have an important task: to develop methodologies to evaluate the impact of programs on functional indicators such as cognition, behavior, development, etc. in infants and children. This information would be very important to better define future strategies and goals for large-scale public health interventions.

Anemia can be an indicator of poor nutrition and/or of poor health. Thus, the complex etiology of anemia, and the difficulties related to accurate diagnosis of iron deficiency, are important considerations when establishing strategies to combat iron deficiency and IDA in many regions. Iron deficiency is a major factor in the etiology of nutritional anemia and interventions to increase iron intake and to improve iron bioavailability are important strategies to combat anemia. In addition, in many settings malaria control and deworming can reduce the prevalence of anemia significantly, as discussed by Drs. Molyneux and Drake. Thus, a holistic approach is needed to combat anemia, iron deficiency, and IDA—including improved sanitation, access to health care, and overall better nutrition. This approach clearly requires a firm commitment from colleagues in a number of sectors and stresses the need for integrated programs. Only by recognizing the complexity of this public health problem, can realistic strategies and goals for the real world situation be established and progress be made.

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Abstracts of Posters presented at the INACG Symposium

1 **EVALUATION OF FILTER PAPER BASED DRIED SERUM SPOTS (DSS) FROM CAPILLARY (Cap) AND VENOUS (Ven) BLOOD FOR ASSESSING IRON DEFICIENCY (ID) IN CHILDREN IN COLOMBO, SRI LANKA.** **[1]N. Ahluwalia, [2]A. de Silva, [1]V. Weaver and [2]S. Atukorala. [1]Nutrition Dept., Pennsylvania State Univ., USA; [2]Dept. of Biochem. and Molecular Biology, Faculty of Medicine, Univ. of Colombo, Sri Lanka.**
Background: ID anemia remains a public health problem world-wide. A filter-paper based DSS assay for ferritin (Ft) measurement has been developed (Ahluwalia et al., 1998) for potential field use, which does not require a cold-chain for sample storage up to 4 wk, and yields results similar to traditional method. The collection of Ven serum, however, is impractical in field situations, and may be limited due to cultural and age-constraints. **Aim**: To measure serum Ft in DSS from Cap and Ven blood under field conditions and evaluate their validity vs. traditional method for serum Ft determination. **Methods:** Ven blood (1 mL) and finger-stick Cap blood (0.1 mL) were obtained by a nurse and a trained field-worker, respectively, from apparently-healthy children (n=100; age: 8.9±0.3 y) at school. Blood samples were centrifuged to obtain serum. Ven and Cap DSS were prepared by precise aliquot of 20 μL serum/ spot on filter paper, air-dried, and placed in air-tight plastic bag. An aliquot (100 μL) of Ven serum was frozen and shipped on dry ice to Penn State for Ft analysis by traditional method. DSS samples were shipped to Penn State and analyzed using the spot Ft method (Ahluwalia et al., 1998) using cellulase from *Trichoderma Ressei* at 2 wk from date of collection. **Results:** Ven and Cap DSS Ft correlated strongly with traditional Ft (r=0.88 and 0.86, respectively, p=0.0001). The geometric mean (CI in parentheses) for Ven and Cap DSS Ft and traditional Ft were 26.9 (24.1-29.9), 33.9 (30.8-37.3), and 33.1 (30.2-36.2) μg/L, respectively, and did not differ (p>0.10). On average, Ven DSS Ft values were 5.81 μg/L lower and Cap DSS Ft 0.03 μg/L higher than traditional Ft method. With iron depletion defined as serum Ft <15 μg/L, the Ven and Cap DSS Ft methods corresponded well with the traditional Ft method in classifying children as iron-sufficient (n=94) or iron-deficient (n=6); the sensitivity and specificity for Ven DSS Ft were 100 and 93.8%, respectively, and that for Cap DSS Ft were 80 and 96.8%, respectively. **Conclusion**: Cap and Ven DSS Ft methods provide accurate assessment of iron status. Further, Cap DSS Ft can offer practical means for detecting ID in field settings.
Supported by a grant from ILSI.

2 **DIETARY CONSUMPTION PATTERNS AND IRON STATUS AMONG FEMALE FACTORY WORKERS IN VIETNAM:** Hoang M,[1] Ramakrishnan U,[1] Thuy PV,[2] Berger J,[3] Davidsson L,[4] Flowers C[5] [1]Rollins School of Public Health, Emory University, USA; [2]National Institute of Nutrition, Vietnam; [3]Institute of Research for Development, France; [4]Laboratory of Human Nutrition, Swiss Federal Institute of Technology, Zurich; [5]Division of Hematology, University of Kansas Medical Center (KUMC), USA

Introduction: Southeast Asia has the highest prevalence of anemia in the world, affecting more than 600 million individuals. It is estimated that half of the anemia is due to iron deficiency. In a national survey conducted in Vietnam in 1995, the prevalence of anemia was 45% and 53% among preschool age children (≤ 5 years) and pregnant women, respectively. **Objectives:** To examine the relationship between iron status and dietary consumption patterns of anemic (Hb<120 g/L) and non-anemic (Hb ≥120 g/L) Vietnamese women of reproductive age (17-45 y). **Methods:** The study sample included anemic (n=111) and non-anemic (n=122) non-pregnant women of reproductive age working in garment and textile factories in Hung Yen and Hai Duong Provinces in Northern Vietnam. Iron status was assessed by measuring hemoglobin, serum ferritin, and transferrin receptor in venous blood. A food frequency questionnaire was developed and used to assess the frequency of consumption in the past month of several foods containing iron, enhancers and inhibitors of iron absorption, as well as common foods that could be suitable for fortification. Other data collected included age, height and weight, parity, and age of youngest child. **Results:** Mean hemoglobin was 111.4 g/L and 129.2 g/L in the anemic and non-anemic group, respectively. Iron rich foods such as beef were not consumed within the past month by 57.0% of women. Vitamin C rich foods (oranges, lemons and mangoes) which can enhance Fe absorption were consumed daily by only 11.4% of women (4.8% by anemic and 6.6% by non-anemic women). Analyses are underway for other indicators of iron status and the association between dietary intakes and iron status will be examined along with other correlates. These findings will be useful to target appropriate intervention strategies to reduce anemia in Vietnam. (Supported in part by the Nippon Foundation, the ILSI Center for Health Promotion and the Hubert Fellowship).

3 **DEVELOPMENT OF A FIELD METHOD FOR HAEMOGLOBIN ESTIMATION.** K.V.Rameshwar Sarma, B. Sivakumar and K. Madhavan Nair, National Institute of Nutrition, Hyderabad-500 007, India.

Background: A major limitation in wide application of haemoglobin measurement in evaluating the health status of the population has been the obligatory "volume transfer" necessary for subsequent determination of blood haemoglobin. **Objective:** To identify a simple method free of pipetting errors to measure haemoglobin in community studies. **Pilot Study:** Two extra thick filter papers of Whatman make were chosen after testing for their blood flow property while searching for an ideal paper. Nineteen heparinised blood samples with widely varying haemoglobin and haematocrit values were taken into pipettes and slowly brought into contact with filter papers so as to transfer measured volumes. The characteristics of the air-dried blood spots were monitored. The results indicated that: (i) Blood spots from the papers showed no interference with colorimetric analysis of haemoglobin using Drabkin's solution, (ii) the papers were capable of holding 20-200 μl of blood in a single contact, (iii) the papers possessed uniform spreading properties facilitating predictable relationships between volume applied and area of spread. **Application:** Using one of these papers, intravenous blood samples from adult males, pregnant women and children (n=26) were analysed for haemoglobin both by taking 20 μl of blood directly and punch areas of blood spots equivalent to 15 μl from the established relationship. Both the sets of haemoglobin values were in close agreement validating the volume and area relationships on filter paper. The method was later extended to capillary samples collected from 84 school children. The set of haemoglobin values obtained with spots on filter paper agreed with those derived from 20 μl of blood taken directly. The correlation between the two sets of values was highly significant (r=0.980). **Conclusion:** This may be an ideal method for extensive use in field conditions for community studies for haemoglobin measurement since the measurement errors in pipetting 20 μl of blood are eliminated.

4 IRON AND VITAMIN A STATUS DURING PREGNANCY AND LACTATION DETERMINE IRON AND RETINOL CONCENTRATIONS IN BREAST MILK.
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Maternal nutritional status both before and during pregnancy affects not only birth weight, but also infant growth and mortality later in the first year of life of infants. Breast milk plays a role in this relationship. We investigated the association in mothers between hemoglobin, serum ferritin and serum retinol concentrations at second trimester, near term, and ~4 mo postpartum with iron and retinol concentrations in transitional milk (4 – 7 d postpartum, n = 90) and mature milk (3 mo postpartum, n = 151). The study was carried out among 17-35 y old women in one rural subdistrict in West Java, Indonesia. During pregnancy, the women were allocated to 3 groups: one group (n = 113) received a weekly supplement of iron (120 mg Fe as $FeSO_4$) and folic acid (500 μg); one group (n = 112) received the same amount of iron and folic acid plus vitamin A (4,800 retinol equivalents, RE or 16,000 international units, IU); and one group (the 'daily' group) (n = 116) had access to iron and folic acid supplements from the government program. Transitional milk had ($P < 0.01$) higher concentrations of iron and retinol than mature milk. The weekly vitamin A and iron group had higher ($P < 0.05$) retinol concentrations related to volume and fat content in transitional milk and retinol concentration related to fat content in mature milk than the weekly iron group. Women having low iron stores at second trimester had lower concentrations of iron ($P < 0.01$) and retinol related to volume ($P < 0.05$) in transitional milk. Anemic subjects at ~4 mo postpartum had lower concentrations of iron ($P < 0.01$) and retinol related to volume ($P < 0.05$) in mature milk. Serum retinol concentrations <1.05 μmol/L at ~4 mo postpartum were associated with lower ($P < 0.01$) concentrations of retinol related to volume and to fat content in mature milk. Thus, serum ferritin during pregnancy is a determinant of iron and retinol concentrations in transitional milk, while hemoglobin and serum ferritin and retinol concentrations at ~4 mo postpartum are determinants of iron and retinol concentration in mature milk.

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5 TRANSFERRIN RECEPTOR LEVELS IN A GROUP OF CHILDREN RECEIVING ANTI-MALARIAL DRUG THERAPY.

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Background: Approximately 75% of preschool children in eastern Africa are anemic, mainly because of iron deficiency (ID) and malaria. Serum transferrin receptor (sT*f*R) is a biological marker of ID and unlike other markers of ID not affected by a range of infections and inflammatory conditions. However, the relation between malaria and sT*f*R remains unclear. **Aims:** We conducted a 4-arm community-based randomized double-blinded placebo-controlled trial to identify strategies to control childhood anemia in Western Kenya and to assess the role of sT*f*R in diagnosing ID. **Methods:** Children (0-36 M of age) with mild anemia (Hb 7.0-10.9 g/dL) were randomized into 4 treatment groups. All 4 groups received single-dose sulfadoxine-pyrimethamine (SP) at baseline followed by: [A] SP at 4 & 8 weeks + daily iron (3 mg/kg for 12 weeks), [B] SP at 4 & 8 weeks + daily placebo iron, [C] placebo SP at 4 & 8 weeks + daily iron for 12 weeks, [D] placebo SP at 4 & 8 weeks + daily placebo iron. All study drugs were given under supervision. Village monitors collected morbidity data and blood samples or smears from enrolled children. We measured sT*f*R in serum collected from the 4 groups (N=650) at baseline, 3, 6, and 12 M follow-up by a commercially available enzyme immunoassay. The normal range of sT*f*R for children (1 year) is 4.5-11.1 ug/mL. **Results:** We grouped the data based on sT*f*R levels (<4.4, 4.5-11.1, and >11.2 ug/mL), the time of each follow-up visit (baseline, 3, 6, and 12 M), and the study group. At baseline, 23-38% of all children had elevated sT*f*R levels. The proportion of children with elevated sT*f*R levels fell slightly in the control group [D] (24% to 15%), but decreased markedly in the 3 other groups [A] (38% to 0%), [B] (33% to 2%), and [C] (23% to 2%) by 6 M. **Conclusions:** Treatment with daily iron supplements as well as with intermittent SP was efficient in lowering the prevalence of ID and malaria associated anemia in these children. We will discuss the relationship between sT*f*R concentrations and malaria, and the role of sT*f*R in interpreting the results of this intervention study.

6 DIFFERENCES IN THE ESTIMATED PREVALENCE OF ANEMIAWHEN ASSESSED WITH THE DIRECT CYANMETHEMOGLOBIN METHOD, THE INDIRECT CYANMETHEMOGLOBIN METHOD OR THE HEMOCUE METHOD

Mayang Sari, Saskia de Pee, Elviyanti Martini, Susilowati Herman, Sugiatmi, Ray Yip, Martin W Bloem. Helen Keller International/Indonesia, NRDC, Bogor, Indonesia, UNICEF, China.

Background: Anemia continues to be a major public health problem, particularly in developing countries. The anemia prevalence estimated depends on the method used for assessing hemoglobin concentration (Hb), and on the cut-off level applied. **Aims:** This study was conducted to compare the results of conventional cyanmethemoglobin, indirect-cyanmethemoglobin (blood stored on filter paper and re-dissolved in laboratory), and HemoCue method. **Methods**: Methods were applied to venous and capillary blood from the same mothers in Indonesia (n=121). **Results:** The indirect-cyanmethemoglobin method found a prevalence of anemia of 31-38%, while the direct-cyanmethemoglobin and the HemoCue method found 14-18%. The indirect-cyanmethemoglobin also had the highest CV and the largest SD of the difference between the first and second assessment of the same blood sample (10-12 g/L versus 4 g/L for direct-cyanmethemoglobin method). Compared to the direct-cyanmethemoglobin method applied to venous blood, sensitivity and specificity of the HemoCue were highest when applied to venous blood (82.4 and 94.2%, respectively). **Conclusion:** Where field and local conditions allow Hb concentration could be assessed with the gold standard, the direct-cyanmethemoglobin method. However, for surveys that would involve different laboratories and/or would be conducted under relatively remote conditions, the HemoCue method can be used. Use of the indirect-cyanmethemoglobin method is discouraged, because it largely overestimated anemia prevalence.

7 IRON SUPPLEMENTATION DURING PREGNANCY FOR INITIALLY NON-ANEMIC, IRON REPLETE WOMEN---DECREASED PREVALENCE OF LOW BIRTH WEIGHT INFANTS

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Background: In 1993, the Institute of Medicine recommended testing whether non-anemic women with adequate iron stores require iron supplementation during pregnancy. **Aims:** We compared administration of a daily iron supplement vs. placebo to initially non-anemic, iron replete pregnant women with respect to compliance, side effects, iron status, anemia, and outcome of pregnancy in a prospective, randomized, double-blinded trial. **Methods:** Low-income pregnant women who enrolled before 20 weeks gestation in a public health nutrition program in Cleveland, Ohio, between June, 1995 and September, 1998, were eligible to participate. Of 513 women, 275 were not anemic (hemoglobin $\geq$ 11 g/dL) and iron replete (serum ferritin $\geq$ 20 µg/L). These women were randomly assigned to receive either a monthly supply of capsules containing 30 mg of iron as ferrous sulfate or placebos. We measured hemoglobin and iron status at baseline and at the beginning of the third trimester (28$\pm$4 weeks gestation). We asked women to bring in their bottles monthly, counted the remaining capsules, gave them a new supply, and asked about side effects. We obtained infant birthweight and gestational age at delivery from postpartum records. **Results:** Seventy-one percent (196/275) of the non-anemic, iron-replete women remained in the study until the third trimester. Of these, 88% took more than half of the pills prescribed and 18% reported side effects at one or more visits. The groups did not differ in initial iron status, adherence to supplementation, or reported side effects. Between the initial visit and third trimester, changes in hemoglobin and erythrocyte protoporphyrin were similar, but the mean ($\pm$ SEM) decline in serum ferritin was slightly less among women who received iron (-35 $\pm$ 2.2 µg/L) than among those who received placebo (-42 $\pm$ 3.3 µg/L). The prevalence of iron deficiency anemia (hemoglobin <11.0 g/dL and serum ferritin concentration <12 µg/L) was 13% in the group who received iron and 21% in the group who received placebo (P=0.12). The prevalence of birth weight < 2.5 kg was 14% in the group who received placebo and 5% in the group who received iron (P=0.03); gestational ages were similar. **Conclusion:** Iron supplementation of pregnant women may have benefits beyond better iron nutritional status. The reduction in the prevalence of low birth weight with iron supplementation deserves further assessment.

8 LOW IRON DURING PREGNANCY INCREASES THE RISK OF DELIVERING PRETERM OR SMALL INFANTS

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Background: It is unclear whether better iron status during pregnancy reduces the risk of infants born preterm or small. **Aims:** We examined the risk of delivering infants preterm (<37 weeks gestation), low birth weight (LBW, <2500 g) or small-for gestational age (SGA<10th percentile birthweight for gestational age) associated with low iron stores in early pregnancy and iron intake from supplements. **Methods:** Serum ferritin (ELISA) was assessed before 20 weeks gestation among 404 women enrolled in an iron supplementation trial in Cleveland, Ohio and categorized into low (12 to <20 µg/L) and very low (<12 µg/L) levels. Women were randomized to receive capsules containing either 30 or 60 mg of iron as ferrous sulfate daily or placebos at three points during pregnancy. We asked women to bring in their bottles monthly, counted the remaining capsules, and gave them a new supply. Total iron intake from supplements throughout the entire pregnancy was categorized into <2.5 g, 2.5 g to <5 g, 5 g to <7 g, and $\geq$7 g (referent group). We calculated adjusted odds ratios (AOR) for preterm, LBW, and SGA infants using multiple logistic regression models with initial serum ferritin levels and total iron intake from supplements controlling for age, race/ethnic group, parity, pre-pregnancy weight, and weeks gestation at initial measurement. **Results:** Compared to women with 7 g or more of iron intake from supplements during pregnancy, the AOR of delivering preterm was 12.0 (95% CI, 2.4-59.4) among women with <2.5 g of iron intake from supplements. The AOR of delivering SGA infants was 7.8 (95%CI, 2.2-27.5) and the AOR of delivering LBW infants was 33.7 (95% CI, 3.6-338.3) among women with < 2.5 g of iron intake from supplements. Compared to women with serum ferritin $\geq$ 20 µg/L, the AOR for delivering preterm infants among women with serum ferritin <12 µg/L was 3.2 (95% CI, 1.03-10.1). Very low iron stores before 20 weeks gestation were not significantly associated with delivery of LBW or SGA infants. **Conclusions:** These findings highlight the importance of adequate iron stores early in pregnancy and iron intake during pregnancy to prevent adverse birth outcomes.

9 **COGNITIVE AND BEHAVIORAL EFFECTS OF IRON DEFICIENCY ANEMIA IN MOTHERS.** E. Perez[1], M. Hendricks[1], A.Berg[2], J.Irlam[1], M Tomlinson[2], W.Abrahams[1], A.Sive[3], L. Feagans[4], J.Beard[4]. [1]Child Health Unit, [3]Red Cross Children's Hospital Department of Pediatrics and Child Health, University of Cape Town; [2]Child and family Unit, University of Cape Town; [4]Pensylvania State University.

INTRODUCTION: It is estimated that 50% of women of reproductive age are iron deficient (WHO 1992). Although iron deficiency anaemia results in impaired cognitive and behavioural effects in infants and young children, much less research has focused on its effects in adults. **AIM:** To assess the impact of iron deficiency anaemia on the cognitive and behavioral performance of mothers, the mother-child interaction and the physical and neuropsychologic development of their infants.

METHODOLOGY: This was a prospective randomized double blind controlled intervention, which included 3 groups of mothers: a control non-anemic group and two anemic groups (one on placebo and one on iron therapy). The assessment of haematologic and iron status, socio-demographic variables and general intelligence (Ravens test) was done at the first visit to a local authority clinic at 6 weeks postpartum. Mothers were assigned to the 3 different groups when their infants were 10 weeks old. At this visit a baseline assessment was done of the mothers' cognitive function and emotional characteristics, the mother-child interaction and the physical and psychological development of the infants. Mothers were followed for 6 months and the same battery of tests repeated when their infants were 9 months old. This is a report on the baseline data. **FINDINGS:** At baseline 95 mothers were included: 33 controls (group C), 32 anemic mothers on treatment (group B) and 30 anemic mothers on placebo (group A). The hematological profiles were: hemoglobin (G/dl) 10.8 (A and B) Vs 13.6(C), MCV 86 fl (A and B) Vs 90.8 fl (C), transferrin saturation 8.6% (A and B) Vs 27.4% (C), serum ferritin 17.1ng/ml (A and B) Vs 56.1 ng/ml(C). There was no significant difference between anemic and control mothers in terms of: age in years 23.1 (A and B)Vs 23.2(C), monthly income (R886, 6 Vs R76 9.6) and education (48% of anemic and 40% of control mothers had 5 years or less schooling). There was no significant difference in marital status (married 42.6% Vs 45%). They had similar results on the Ravens, EPDS (depression), Spielberger (anxiety), and Digit Symbol (attention and general processing speed) tests. There was no statistically significant differences in the way the mothers behaved towards their infants, though there was a tendency for the anaemic mothers to be more controlling but less responsive to their babies. Infants in both groups of mothers had similar birth-weights, heights, head circumferences and Apgar scores. At the 10 week visit there was no difference in physical development of the infants, but infants whose mothers were anemic performed significantly worse on the Griffith's developmental test compared to infants of mothers in the control group (mean GQs of 100.3 vs109.7; $p<0.03$).

10 IRON AND VITAMIN A SUPPLEMENTATION DURING GESTATION AND GROWTH OF INDONESIAN INFANTS.

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Growth faltering during infancy is associated with higher risks of morbidity, mortality and retarded development and may partly be caused by inadequate maternal nutrition during the gestation period. This study was designed to investigate whether infant growth during the first year of life can be improved by supplementation with iron and vitamin A during gestation. Length and weight of infants were assessed monthly and biochemical parameters ~4 mo postpartum. Mothers of these infants from 5 villages had been randomly assigned on an individual basis to double-blind weekly supplementation with 120 mg iron (as $FeSO_4$) and 500 µg folic acid with or without 16,000 IU vitamin A from ~17 wk of pregnancy until delivery; supplement intake was supervised. A third group of mothers from 4 other villages, who received tablets with the same amount of iron and folic acid through the government program, was also recruited. Their tablet intake was not supervised; only 17% took ≥90 tablets and 43% took <30 tablets. Infant length and weight at 0 to 12 mo and increase of length and weight in 12 mo did not differ among the three groups (n ≥70 per group). Neonatal weight and length of boys (3.2 kg; 49.5 cm) was higher ($P<0.05$) than those of girls (3.1 kg; 48.9 cm). Boys also increased their weight and length (by 5.3 kg and 22.8 cm) more ($P<0.01$) than girls (4.9 kg; 21.6 cm) in 12 mo. Hemoglobin, serum ferritin and serum soluble transferrin receptor concentrations at ~4 mo postpartum (mean: 3.7 mo; range: 1.9–6.3 mo) did not differ among the three groups. The proportion of infants with a hemoglobin concentration <100 g/L and <110 g/L was similar in all groups, 29% and 68% respectively. Only three infants had a serum ferritin concentration <12 µg/L. Both neonatal weight and length were associated with hemoglobin and serum ferritin concentrations. Weight and length increase was similar in anemic and non-anemic infants. Serum ferritin concentration was inversely correlated with weight and length increase in 12 mo, reflecting the decline of iron stores during the first months of life when body iron is mobilized for growth. Girls had a better iron status defined by higher serum ferritin and lower soluble transferrin receptor concentrations than boys, which might be explained by the difference in growth rate. In conclusion, in this study iron and vitamin A supplementation during the gestation period did not benefit growth of Indonesian infants during the first year of life.

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11 **LOW-DOSE ORAL IRON IMPROVES LANGUAGE AND MOTOR DEVELOPMENT OF AFRICAN PRESCHOOLERS.**

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Background. Iron deficiency anemia is associated with alterations in child development, but a causal relationship has not been proven. The relation of helminth infection to early child development has not been examined. **Aims.** To find out if iron supplementation or deworming can improve child development in a context where anemia is severe and stems from multiple etiologies. **Methods**. A community-based sample of 614 children in Pemba Island, Zanzibar were randomly allocated to 10 mg/d oral iron or placebo and 500 mg quarterly mebendazole or placebo for a 12-month period. Severely anemic children were treated therapeutically for 1 month and otherwise kept on protocol. Child development was assessed by parental interview pre- and post-treatment in age-appropriate subgroups (n=359 for language and 247 for motor assessment). **Results**. Before intervention, anemia was prevalent and severe. Geohelminth infections were prevalent and light. *P. falciparum* infection was nearly universal. Iron significantly improved iron status but not hemoglobin. Iron improved language development by 0.6 points (95% CL: 0.1, 1.2) on a 20-point scale. Iron's effect on motor development was modified by baseline hemoglobin (p=0.014) and was apparent only in children with hemoglobin <90 g/L. At baseline hemoglobin 68 g/L (1 SD below the mean value), the iron treatment effect was 1.1 points (0.1, 2.1) on an 18-point scale. The treatment effects of mebendazole were 0.4 points (-0.3, 1.1) on the motor scale and 0.3 points (-0.3, 0.9) on the language scale. **Conclusions**. Iron supplementation but not mebendazole significantly improved motor and language development of rural African preschoolers. The findings suggest that iron deficiency (not anemia) causes language deficits, while severe iron deficiency anemia causes motor deficits. (Funded by Thrasher Research Fund and USAID Office of Health and Nutrition.)

12 A NEW METHOD FOR ESTIMATING MATERNAL MORTALITY ATTRIBUTABLE TO SEVERE ANAEMIA DUE TO NON-MALARIAL FACTORS.

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Background: Direct estimates of anaemia and pregnancy related maternal mortality are available from hospital studies with estimates varying between 1% and 46% of maternal deaths. There is little documentation on the criteria for these clinical judgements or the specific causes of anaemia, which for many of these cases would be multifactorial. There are no randomised controlled trials of iron interventions to reduce anaemia in pregnancy with mortality as an outcome variable. Such a trial would be contentious for ethical reasons. Indirect methods are therefore required for estimating cause-specific maternal mortality. A new indirect method is described for distinguishing malarial from non-malarial causes of maternal mortality. Most of the non-malaria factors can be attributed to nutritional deficiency and a large component of this is iron deficiency.

Method: The initial step is to estimate the malaria-attributable component of severe anaemia (Hb <7g/dl) in primigravidae (PAR^m). This estimate is derived from a calculation which assumes that the excess risk of anaemia in first compared to later pregnancies is attributable to malaria. This is because women in their first pregnancy have much higher susceptibility to malaria than women of higher parity. Cause specific mortality in primigravidae related to severity of anaemia can be then calculated using the formula:

$P \times (PAR^m) \times (CFR)$ = maternal mortality from malaria anaemia
$P \times (1 - PAR^m) \times (CFR)$ = maternal mortality from non-malarious anaemia

Where P is the prevalence of severe anaemia, PAR^m and $(1 - PAR^m)$ the population attributable risk estimates respectively for malarial and non-malarial severe anaemia in primigravidae and CFR the case fatality, which is derived from hospital mortality data for all cause anaemia. Using this formula in a holoendemic malarious area with a 5% severe anaemia prevalence (Hb<7g/dl), and a 1% case fatality rate, there would be 9 severe malaria anaemia related deaths per 100,000 livebirths in first pregnancies and 41 non-malarial anaemia-related deaths. Corresponding values can be calculated for different values of severe anaemia prevalence.

13 EFFECTS OF IRON SUPPLEMENTATION ON HAEMOGLOBIN AND MORBIDITY IN CHILDREN WITH UPPER RESPIRATORY TRACT INFECTION. **[1]Angela de Silva, [1]Sunethra Atukorala, [2]Irangani Weerasinghe, and [3]Namanjeet Ahluwalia. [1]Department of Biochemistry and Molecular Biology, Faculty of Medicine, University of Colombo, Sri Lanka [2]Lady Ridgeway Children's Hospital, Colombo, Sri Lanka, [3]Nutrition Department, The Pennsylvania State University, USA.**

Background: Increased susceptibility to infection is a major problem in children with iron deficiency. **Aims:** A study was conducted to evaluate the impact of iron supplementation on haemoglobin (Hb) concentration and morbidity in children with infection (INF), or without infection (CTRL). **Study Design:** Children aged 5-10 years (n=332) were recruited from the Out Patients Department, Children's Hospital, Colombo, Sri Lanka for a randomised controlled, double blind study and randomly supplemented with iron (60 mg $FeSO_4$) or placebo once daily for 8 weeks. Morbidity, clinical and inflammatory status, anthropometry and Hb were assessed at baseline and post intervention and children grouped into INF (n=154) or CTRL (n=178). Children with a past history of recurrent upper respiratory tract infection (URTI) and evidence of current URTI, with elevation of ≥ 3 inflammatory criteria were included in the INF group. Controls were those without infection. The INF group was subdivided depending on whether they had infection at both baseline and post intervention (INF1 Y1Y2: n=48) or only at baseline (INF2 Y1N2: n=106). Morbidity and compliance were recorded once every 2 weeks. **Results:** High compliance was noted with iron (95 %) or placebo (97 %). Regression analysis indicated that after controlling for baseline Hb, folate, vitamin B_{12}, change in inflammatory parameters and anthelminthic therapy, iron supplementation had a significant positive effect on Hb (p=0.000) and reduced (p=0.000) the prevalence of anaemia from 62 to 27 %, 55 to 33 % and 54 to 34 % in INF1 Y1Y2, INF2 Y1N2 and CTRL groups respectively. No significant change was seen in placebo groups.Children in INF2 Y1N2 group supplemented with iron had a significant reduction in number of morbidity episodes (Iron: 1.59 ± 0.7, Placebo: 2.73 ± 0.8. p=0.000) and median duration of illness (Iron: 10, Placebo:28 days p=0.000) .In INF1 Y1Y2 , the mean number of illness episodes (Iron: 3.20 ± 0.7, Placebo: 3.42 ± 0.9, p=0.3) and median duration of illness (Iron: 27.5, Placebo: 30.5 days, p=0.1) indicated a trend towards reduced morbidity in iron supplemented children. Iron supplemented children in CTRL group too had a significant reduction in mean number of illness episodes (Iron: 0.92 ± 0.7; placebo: 1.36 ± 1.0, p=0.001) and median duration of illness (Iron: 5, placebo: 8 days, p=0.001). **Conclusion:** Iron supplementation increased Hb and reduced morbidity due to URTI in children with or without infection. This study was supported by a grant from ILSI, USA.

14 SEVERE ANEMIA DURING PREGNANCY IS ASSOCIATED WITH INCREASED RISK OF NEONATAL DEATH IN NEPAL. ML Dreyfuss, J Katz, RJ Stoltzfus, SC LeClerq, EK Pradhan, SK Khatry, SR Shrestha, KP West, Jr. Center for Human Nutrition, The Johns Hopkins University, Baltimore, MD, USA and Nepal Netra Jyoti Sangh, Kathmandu, Nepal.

Severe anemia during pregnancy increases the risk of maternal death in developing countries, but whether it also contributes to increased risk of neonatal death is not well understood. We enrolled and prospectively followed a community-based cohort of pregnant women participating in a randomized vitamin A supplementation trial in rural Nepal to examine whether pregnancy anemia was associated with an increased risk of neonatal death. Upon becoming pregnant, women were invited for a clinical health exam including assessment of iron status, nutritional status, and infections. Pregnancy outcome and infant vital status were ascertained from a community-based monitoring system and subsequently confirmed by trained interviewers. Pregnancy iron status was assessed by hemoglobin (HB) and serum ferritin (SF) at ~19 weeks gestation. Neonatal deaths were defined as live births that died at ≤28 days. Twin births were excluded. The prevalence of any anemia (HB<110 g/L), moderate to severe (HB<90 g/L), and severe (HB<70 g/L) anemia was 70%, 20%, and 4%, respectively. Fifty-six percent had low iron stores (SF<10 µg/L). Among 1081 singleton live births, there were 59 (5.4%) neonatal deaths and the rate did not differ by supplement group. The median age of death was 2 days. The neonatal death rate increased with decreasing HB (χ^2 test for trend, P<0.05) and this trend was primarily attributable to the high rate among severely anemic women. For HB categories of ≥110, 90-109, 70-89, and <70 g/L, neonatal death rates were 3.6%, 6.0%, 5.1%, and 14.6%, respectively. Risk of neonatal death was not increased among women with low iron stores, poor nutritional status (low weight or height), malaria, or hookworm infection, but primiparity, reported severe illness in late pregnancy, and preterm birth (gestational age<37 wk) were associated with significantly increased risk of neonatal death. In a multivariate model adjusting for these significant risk factors as well as gestational age at enrollment and supplement group, severe anemia was associated with a significantly increased relative odds of neonatal death compared to non-anemic women (AOR=4.6, 95% CI: 1.4, 14.6). The risk among women with mild and moderate anemia was also increased, but the confidence intervals for the odds ratios included one. These data provide further evidence of the serious health consequences of anemia during pregnancy for women and their infants in South Asia. (Supported by the Office of Health & Nutrition,USAID, Wash DC and the Sight and Life Institute at Johns Hopkins University)

15 EFFECT OF IRON SUPPLEMETATION ON THE INCIDENCE OF INFECTIONS IN CHILDREN : A SYSTEMATIC REVIEW

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Background: Recently concerns have been expressed regarding the safety of iron supplementation in children because of a higher documented risk of infections in some studies. A systematic review was therefore planned to address this issue. **Aims:** To evaluate the effect of iron supplementation in children on the incidence of individual and total infectious morbidities. **Methods:** The review included randomized controlled trials involving supplementation of iron through oral or parenteral route or in the form of iron fortified feeds or cereals. The RCTs were identified by searching computerised databases (MEDLINE, COCHRANE, EMBASE, IBIDS, Healthstar) from the citations listed in the identified trials and consulting investigators. To avoid publication bias authors of unpublished studied were also contacted and such RCTs included. The morbidities studied were respiratory tract infection, diarrhea, malaria, other infections (septicemia, cutaneous infections, worm infestations, tuberculosis etc.) and the total recorded infections. The pooled estimates of incidence rate ratio (IRR) were calculated by the random effects model. **Results:** A total of 24 RCTs on 7438 children, which included 5 unpublished studies and 19 published ones, were identified for the final analysis. No significant publication bias was evident on plotting. The incidence of all evaluated morbidities was marginally increased in the iron supplemented children but the differences were not statistically significant (p>0.05) - malaria [IRR=1.13 (CI= 0.92, 1.39)], respiratory tract infection (IRR= 1.02, CI= .95, 1.10), diarrhea (IRR= 1.09, CI= .99,1.21), other infections (IRR= 1.02, CI= .94, 1.10) and total recorded infections (IRR= 1.04, CI=.98, 1.09). Various sensitivity analysis did not alter the inference. **Conclusions:** Iron supplementation does not result in a significantly higher risk of infections in children.

16 HIV infection and post-partum anaemia

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Background: Current literature suggests that the risk of anaemia in pregnancy is increased with maternal HIV infection. These studies, however, did not evaluate the effect of HIV on post-partum anaemia (PPA). **Aims**: To determine the prevalence of PPA and associated risk factors including maternal HIV infection. **Methods**: 306 women, were enrolled into a longitudinal HIV mother to child transmission study at the University Teaching Hospital, Lusaka, Zambia. Hb, MCV, PCV, CD4 cell count were measured within 24 hours of delivery and HIV serology, RPR and serum retinol were estimated. Maternal haemoglobin was measured a month after delivery. Information on maternal characteristics was collected at enrolment. **Results**: 143 (46.7%) women were anaemic and in 19 (6.2%) anaemia was severe. HIV infection was present in 30.1% women and was independently associated with PPA (OR 2.81; 95% CI 1.34-5.90), but not viral load, CD4 cell count or percentage. 36 (12.1%) of the 306 women had caesarean section, of which 6 were elective. Caesarean section (elective and emergency) significantly increased the risk of PPA (OR 9.95; 95% CI 2.83-34.96) after correcting for other variables. 12.8% of the women had serum retinol <20µg/dl and low serum retinol was independently associated with increased risk of PPA (OR 3.03; 95% CI 1.09-8.42). Other factors associated with PPA were post-natal anaemia (1.98; 95% CI 1.46-2.68), alcohol intake (0.22; 95% CI 0.07-0.7) andpost-partum maternal weight (0.10; 95% 0.01-0.74), MCV (2.39; 95% CI 1.18-4.82) and MCHC (8.33; 95% CI 3.87-17.95). **Conclusion**: PPA is a common problem and it's association with maternal HIV infection, post-natal anaemia, caesarean section and low serum retinol has important public health implications.

17 DOES MULTIPLE MICRONUTRIENT SUPPLEMENTATION INCREASE HEMOGLOBIN AND IRON STATUS MORE THAN IRON ALONE?

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In a previous study in rural Mexico we found that Hb concentrations of anemic preschoolers were not significantly greater than controls after 12 months of daily supplementation with 20 mg iron. In the present study we compared Hb and ferritin response to supplementation with other micronutrients commonly deficient in this population, with response to iron alone. In a longitudinal, double-blind, placebo controlled study, 125 anemic children age 12 to 40 months were assigned to 1 of 4 groups; A) ferrous sulfate, B) ferrous sulfate and vitamin B12, C) Ferrous sulfate and vitamins B2, B12, A, B6, E, folate, zinc and copper, or D) placebo. Supplements were given 3 days a week for 3 months, at twice the RDA, under supervision. At 0 and 3 months measures included Hb, ferritin, serum A, E, B12, CRP and folic acid and plasma zinc. Morbidity was assessed at each visit. Change in Hb (mean ± SEM) was 14 ± 2.9, 11 ± 2.6, 5.6 ± 1.5, and 4.8 ± 1.6 g/L in groups A, B, C and D respectively. The change in groups A, B and C was significantly greater than in the placebo group but the response in A, B and C was similar (ANOVA controlling for initial values). Children in groups A and B had significantly more episodes of respiratory disease, but not diarrhea, compared to group D ($p<0.01$). The multiple micronutrient supplements did not improve anemia or iron status more than iron alone. (Supported in part by UC Mexus).

18 WEEKLY IRON-FOLATE SUPPLEMENTATION IN WOMEN IN REPRODUCTIVE AGE IN VIETNAM : A NEW APPROACH TO CONTROL IRON DEFICIENCY ANEMIA DURING PREGNANCY.

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Background: In Vietnam, prevalence of anemia is 40% in women of reproductive age and 53% in pregnant women despite a national iron-folate supplementation program for pregnant women. **Aim of the study:** To evaluate the effectiveness of a new preventive approach to control iron deficiency anemia in women of reproductive age and during pregnancy by weekly iron-folate supplementation. This approach will be compared with daily iron-folate supplementation of pregnant women. **Method:** 701 women of reproductive age, nulliparous and willing to have a baby, and 164 pregnant women were included in the study. At the beginning of study a social marketing and mobilization campaign was initiated to educate women about the importance of iron-folate supplementation throughout their reproductive life. Weekly iron-folate supplements (60 mg iron + 3.5 mg folate), especially produced for the study by a private factory, were sold to the non-pregnant women by the Women Union. When pregnancy was detected, the women received free weekly iron-folate supplements containing double dose of iron. Women pregnant at baseline received a free daily iron-folate supplementation (60 mg iron and 0.25 mg folate). Knowledge, attitude, behavior and practice (KABP) and iron status (hemoglobin, ferritin) of women were evaluated at baseline and 4.5, 9 and 12 months later. **Results:** The social marketing and mobilization campaign was effective to improve KABP in all women, if pregnant or not. Few side effects were reported and compliance was high. At the end of the study, most women were willing to continue with weekly supplementation. Concerning iron status, preliminary results do not show significant differences between weekly and daily iron-folate supplementation during pregnancy. The effect of duration of weekly iron-folate supplementation intake before the beginning of pregnancy on iron status during pregnancy is currently under analysis.

19 THE EFFECT OF β-CAROTENE, ZINC AND IRON SUPPLEMENTATION IN INDONESIAN INFANTS ON MICRONUTRIENT STATUS AND GROWTH.

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Background: Deficiencies of vitamin A, iron and zinc are prevalent worldwide. However, the existence and consequences of concurrent deficiencies have received little attention. This study is part of an UNICEF-initiated multi-country collaboration of iron and zinc supplementation trials. **Aims:** To investigate the effects of β-carotene, iron, and zinc supplementation, combined and separate, on the growth and micronutrient status of young infants. **Methods:** A randomized double-blind supplementation trial was done in 607 infants (mean age 4.2 months, range 2.8-5.8) in Bogor District, Indonesia. Six groups were supplemented on weekdays for six months with either β-carotene (2.4 mg), β-carotene+zinc combined (2.4 and 10 mg), zinc (10 mg), iron (10 mg), zinc+iron combined (10 mg and 10 mg), or placebo. Growth of the infants was monitored monthly. Morbidity was recorded daily by village health workers, and checked with a two-weekly recall. A venous blood sample was obtained at the end of the study, and iron supplementation given to all anemic infants. **Results:** A total of 444 infants completed the trial (mean age 10.1 months, range 8.6-11.6). Anemia (Hb<110 g/L), and iron deficiency (anemia and ferritin<10 µg/l) are very prevalent in this population (67% and 31% resp. in the placebo group). Both iron and zinc+iron supplementation significantly reduced anemia and iron deficiency (prevalence 4% and 5% resp, $p<0.01$, Chi-square). However, β-carotene supplementation also positively affected hemoglobin concentrations ($p<0.05$, R=0.10, multiple regression), whereas zinc supplementation had a negative effect ($p<0.05$, R=-0.10, multiple regression). Plasma zinc concentrations were increased after zinc supplementation ($p<0.01$, R=0.24, multiple regression). Plasma retinol and β-carotene concentrations are currently being analyzed, and the data will be presented, as well as morbidity data. The anthropometry of the infants showed a striking decrease in Z-scores during the study period in all groups (total increments: weight for age Z score −1.24, height for age Z score −0.45, weight for height Z score −1.12). However, the decrease in Z-scores was significantly less in β-carotene supplemented infants for height-for-age (mean −0.32 vs. −0.48, $p<0.05$, T-test) and weight-for-age Z-scores (mean -1.11 vs. −1.27, $p<0.05$, T-test). **Conclusions:** Combined micronutrient supplementation can have synergistic effects in improving micronutrient malnutrition, whereas single micronutrient supplementation might adversely affect other micro-nutrients. The growth faltering during the first year of life, also commonly found in other developing countries, was reduced by 33% with β-carotene supplementation.

20 WOMEN'S PERSPECTIVES ON IRON DEFICIENCY: USING QUALITATIVE RESEARCH FROM EIGHT DEVELOPING COUNTRIES TO IMPLEMENT AN ANEMIA PREVENTION AND CONTROL PROGRAM.

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Background: The World Health Organization estimates that 58% of pregnant women in developing countries are anemic. In spite of the fact that most ministries of health in developing countries have policies to provide pregnant women with iron in a supplement form, maternal anemia prevalence has not declined significantly where large-scale programs have been evaluated. In addition, women's lack of compliance with taking iron tablets has been suggested as the reason for the lack of success of these programs. **Research:** From 1991-1997, the MotherCare Project and its partners conducted qualitative research to determine the major barriers and facilitators of iron supplementation programs for pregnant women in 8 developing countries. Research results were used to identify barriers and facilitators and then to develop pilot programs, including communication and behavior change strategies, to reduce maternal anemia. **Findings:** While women frequently recognize signs and symptoms of anemia, they often do not consider it to be a priority health concern that requires action. Those women who access prenatal health services are often more familiar with iron supplements, but commonly do not know why they are prescribed. Contrary to the belief that women stop taking iron tablets mainly due to side effects, only about one-third of women reported that they experienced negative side effects in these studies. During iron supplementation trials in 5 of the countries, only about one-tenth of the women stopped taking the tablets due to side effects. Barriers to effective supplementation programs include deficient counseling and distribution of iron tablets, inadequate supplies of supplements, poor utilization of prenatal health care services, and cultural beliefs against consumption of pharmaceuticals during pregnancy. Facilitators include women's recognition of improved physical well being with the alleviation of symptoms of anemia, increased appreciation of benefits for their baby, and subsequent increased demand for prevention and treatment of iron deficiency and anemia. **Program:** These findings were used to develop educational materials, messages, and a community-based iron distribution strategy. Examples of how the research findings informed the development and implementation of the MotherCare anemia prevention and control program, including IEC materials developed for individual country programs, will be presented at INACG.

21 **COMPREHENSIVE APPROACH TO REDUCE ANEMIA IN PREGNANT WOMEN.** **Robert Mwadime, RCQHC, Makerere University, Kampala Uganda; Phil Harvey, MOST/USAID; Lonna Shafritz, CHANGE/AED, Washington, USA.**

Problem Addressed: There is a lack of programs proven effective in treating anemia. Research suggests that the limited effectiveness results from a) problems in accessibility and continuity, and quality of antenatal services which contributes to low compliance by clients, and b) interventions that do not comprehensively treat the causes of anemia. This proposed program is based upon the premise that *an effective anemia control program must address all the primary causes of anemia.* Causes vary, for example, in tropical Africa malaria and hookworm, as well as diet deficient in bioavailable iron are known to be major determinants of hemoglobin status. **Objective:** Improve antenatal services with the aim of reducing moderate-severe anemia. **Program Design:** Undertake a rapid situational analysis that includes 1) synthesis of existing data relating to causes of maternal anemia, and 2) innovative methods to determine current knowledge, attitudes and practices of health workers and clients to anemia and antenatal care. The results of this multi-dimensional input will be used to develop a comprehensive antenatal care package to be implemented at the system, the provider, and the client levels. *Systems level:* 1) ensuring availability of iron/folic acid, malaria drugs, deworming treatments, IEC, job aids, etc; 2) providing supportive supervision; 3) strengthening the link between health facilities and community; 4) strengthening sustained institutional commitment to addressing this problem. *Provider level* -- a training package with priority on screening, behavior change, and communication skills; strategies to enhance motivation and ownership of the intervention. *Client level* -- a communication package informing clients of their rights to quality services, the importance of antenatal services to clients' health, and addressing any behavioral barriers/ enablers related to compliance and satisfaction. **Evaluation methods:** A quasi-experimental design using pre-test and post-test comparisons between two or three intervention districts and one control district is suggested. Indicators will include both process and outcome components (including the prevalence of moderate-severe anemia; client compliance; provider compliance; client-provider interaction; and empowerment of clients). **Expected Project outputs** include: guidelines for designing comprehensive anemia interventions; training modules and job aids; communication strategy and materials; and most importantly: a field-tested 'comprehensive antenatal nutrition package' including a strategy for scaling up/expansion.

22 **EFFECTS OF IRON SUPPLEMENTATION OF BREAST-FED INFANTS IN HONDURAS AND SWEDEN FROM 4-9 OR 6-9 MO OF AGE.**

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Background: Iron drops are often recommended for breast-fed infants after 6 mo of age if they do not consume adequate amounts of iron-fortified complementary foods. It has recently been proposed that this practice should start at 4 mo of age. However, neither approach has been evaluated adequately. **Aims:** To evaluate the effects of iron supplementation of breast-fed infants on hemoglobin (Hb) and several indicators of iron status, growth and morbidity in two populations with differing social and nutritional status. **Study design**: We randomly assigned term Swedish (n=101) and Honduran (n=131) infants to 3 groups at 4 mo of age: 1) Iron supplements, 1 mg/kg/day from 4-9 mo, 2) placebo 4-6 mo and iron 6-9 mo, 3) placebo 4-9 mo. All infants were breast-fed exclusively to 6 mo and partially to 9 mo. **Results**: From 4-6 mo, the effect of iron was significant and similar in both populations for Hb, ferritin and ZPP. From 6-9 mo, the effect was significant and similar at both sites for all iron status variables except Hb, for which there was a significant effect only in Honduras. In Honduras, the prevalence of iron deficiency anemia (IDA) at 9 mo was 29% in the placebo group and 9% in the supplemented groups. In Sweden, iron supplements caused no reduction in the already low prevalence of IDA at 9 mo (<3%). Length gain was significantly lower in infants given Fe supplements, and among infants with Hb > 110 g/L at 4 mo, diarrhea was more common than in those given placebo. **Conclusions**: Iron supplementation from 4-9 or 6-9 mo significantly reduced IDA in Honduran breast-fed infants. However, while Fe supplemention can improve Fe status and reduce anemia in socioeconomically disadvantaged populations where IDA is prevalent, this can also lead to negative consequences, warranting a cautious approach. (Supported by USDA and Trasher Research Fund)

23 **CONTROL OF IRON DEFICIENCY ANEMIA IN VIETNAMESE INFANTS BY EFFICACY OF IRON AND ZINC SUPPLEMENTATION TO REDUCE ANEMIA AND GROWTH FALTERING IN VIETNAMESE INFANTS.** NX Ninh[1], J Berger[2], M Tolvanen[3], NQ Trung, NV Nhien[1], DK Lien[1], T Quyen[1], NC Khan[1], HH Khoi[1]. [1]National Institute of Nutrition (NIN), Hanoi, Vietnam, [2]the Institute of Research for Development (IRD), France and [3]UNICEF, Vietnam.

Background: In Vietnam, anemia and stunting faltering are prevalent in infants. Both iron and zinc supplementation are required in areas where there is no immediate solution for a dietary approach. However, the efficacy of a combined zinc-iron supplementation must be evaluated before large scale implementation. **Aims:** To evaluate the efficacy of daily iron and zinc supplementation in preventing iron deficiency anemia and growth faltering in Vietnamese infants. **Methods:** 916 infants aged from 4-7 months were randomly divided into 4 groups. Group 1 received a daily dose of 10 mg iron, Group 2 a daily dose of 10 mg zinc, Group 3 a daily dose of 10 mg iron and 10 mg zinc and Group 4 a placebo. Iron and zinc status were measured at baseline (T0) and six months later (T6) whereas anthropometry was measured monthly and morbidity daily. **Results:** After 6 months of supplementation, hemoglobin concentration (Hb) improved in all groups but Hb changes were significantly higher in group 1 (22.8 ± 19.4 g/L) and in group 3 (20.4 ± 19.5 g/L) than in group 2 (6.2 ± 21.4g/L) and in group 4 (9.8 ± 19.3) ($p<0.0001$). Hb change in group 2 was not different from group 4. At baseline, prevalence of anemia was 53.9 %. By T3, anemia prevalence was significantly decreased only in group 1 (8.2%) and in group 3 (8.1%). Serum zinc concentration (Zn) also improved in all groups. However, Zn changes were significantly higher in group 2 (67.0 ± 53.5 µl/L) and in group 3 (52.8 ± 45.0 µl/L) than in group 1 (8.0 ± 19.8 µl/L) and in group 4 (10.5 ± 26.1 µl/L) ($p<0.0001$). Zn change in group 1 was not different from group 4. At baseline, 11.3 % of infants were stunted (Length-for-age Z score, LAZ <-2 SD) and 3.3 % underweight (Weight-for-length Z score, WLZ <-2 SD). By the end of supplementation period deficit in mean LAZ and WLZ increased in all groups but changes in WLZ were significantly lower in group 3. Over the study period, changes in LAZ were not different between groups. All treatments had same effect on LAZ values but proportion of stunting increased less in groups 2 and 3 than in group 4. **Conclusion**: Six-month-daily iron supplementation, either alone or in combination with zinc, had a significant positive effect on hemoglobin concentration and decreased prevalence of anemia to less than 10%. Zinc supplementation, alone or combined with iron, improved serum zinc concentration. Therefore, iron-zinc combined supplementation was effective to improve both iron and zinc status. Iron supplementation had no effect on growth whereas zinc supplementation showed a positive effect on weight and weight-for-length Z score. Analysis of morbidity data, currently in process, are needed for appropriate interpretation of these results.

24 **WEEKLY PREVENTIVE IRON-FOLATE SUPPLEMENTATION IN WOMEN OF REPRODUCTIVE AGE IN VIETNAM : PROJECT ASSESSMENT AND IMPACT EVALUATION.**

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Background: In Vietnam, prevalence of anemia is 40% in women of reproductive age and 53% in pregnant women despite the latter receive free daily iron-folate supplementation when pregnancy is detected. **Aim of the study:** To evaluate the effectiveness of a new preventive approach to control iron deficiency anemia in women of reproductive age and during pregnancy by weekly iron-folate supplementation. This approach will be compared with daily iron-folate supplementation of pregnant women. **Method:** 701 women of reproductive age, nulliparous and intending to have a baby, and 164 pregnant women were included in the study. At the beginning of the study a social marketing and mobilization campaign was initiated to educate women about the importance of iron-folate supplementation throughout their reproductive life. Weekly iron-folate supplements (60 mg iron + 3.5 mg folate), especially produced for the study by a private factory, were sold to the non-pregnant women by the Women's Union. When pregnancy was detected, the women received free weekly iron-folate supplements containing double dose of iron (120 mg). Women pregnant at baseline received the free daily dose of 60 mg iron and 0.25 mg folate. Knowledge, attitude, behavior and practice (KABP) and iron status (hemoglobin, ferritin) of women were evaluated at baseline and 4.5, 9 and 12 months later. **Results:** The social marketing and mobilization campaign was effective to improve KABP in all women, whether pregnant or not. Few side effects were reported. The proportion of women taking regularly the supplements increased from 54% in the first month to about 93% in the following months. At the end of the study, most women expressed their willingness to continue with weekly supplementation. Concerning iron status, preliminary results do not show significant differences between weekly and daily iron-folate supplementation during pregnancy. The effect of duration of weekly iron-folate supplementation intake before the start of pregnancy on iron status during pregnancy will be discussed.

25 IRON SUPPLEMENTATION AND DE-WORMING OF PREGNANT WOMEN IN ORISSA – ASSESSMENT OF COVERAGE AND NUTRITIONAL IMPACT.

Gita Pillai, Rebecca J. Stoltzfus, Constance A. Nathanson, W.Henry Mosley, Bonani Sambal, Alaka Dash, Anju D. Singh.

Background: In India 60% of women are anemic in early pregnancy, and 75% are anemic in their last trimester. Iron supplementation and de-worming have demonstrated efficacy in reducing iron deficiency anemia, and are appealing for their low cost and potential for wide coverage. However less than 20% of pregnant women in India benefit from iron or mebendazole, because they do not receive or consume the tablets. **Aims:** This study tests the effectiveness of a strategy to increase pill intake and reduce the prevalence of anemia. **Methods:** The study applied a pre-test post-test control-group design. Strategy enhancements were promoted only in the project area through existing government or village resources, and included: 1) village-based pill supply, promotion, and monitoring; 2) early pregnancy registration; 3)family reminders and 4) self-monitoring of pill intake. Program evaluation compared 4 independent samples generated from survey data at time 1 (non-project area n=200, project area n=215); and time2 (non-project area n=201 and project area n=226). The samples were drawn from 170 villages of Harichandanpur Block in Keonjhar District of Orissa. **Results:** Iron intake (>7500mg during pregnancy) increased significantly from 10.6% to 35.8% (p=.0005) in the project area, and from 7.6% to 8.0% in the non-project area (p=.88). Mebendazole intake increased dramatically and significantly in the project area from 4.6% to 54.4% (p=.0005); while the change in the non-project area was less dramatic, but statistically significant, from 1.5% to 10.4% (p=.0005). There was a significant decline in the prevalence of anemia (Hb<11) from 86.0% to 70.9% (p=.0005) in the project area, while the change in the non-project area was from 81.8% to 78.5% and not significant (p=.45). **Conclusions:** The results suggest that the prevalence of anemia (Hb<11) can be reduced with regular and accessible supply of iron and mebendazole, daily reminders, and self-monitoring of pill intake. The next challenge is to test the strategy in multiple contexts and at a larger scale in India. **Acknowledgements**: Funding was provided by USAID, Office of Health and Nutrition and Office of Food For Peace, The Earnest Lyman and Hellen Ross Stebbins Scholarship, and The Johns Hopkins University Dept. of Population and Family Health Sciences. It was implemented by CARE and designed and evaluated with technical support from JHU.

26 CONTROL OF IRON DEFICIENCY ANEMIA IN VIETNAMESE INFANTS BY WEEKLY AND DAILY IRON SUPPLEMENTATION: EFFICACY AND EFFECTIVENESS.

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Background: In Vietnam, a recent national survey shows that 60% of infants under 2 years of age suffer from anemia. Therefore, implementation of strategy to control iron deficiency anemia in infant is urgent. Weekly iron supplementation has been proven to be efficient in controlled studies in women and school children but was not investigated in infants. **Aims:** To evaluate the efficacy of weekly iron supplementation and the effectiveness of daily iron supplementation in Vietnamese infants. **Methods:** 270 infants aged from 6-12 months were divided into 4 groups. Group 2, 3 and 4 received a daily or a weekly iron dose of 15 mg iron (FeSO4) whereas Group 1 received a placebo (n=68). In Group 2, iron was given daily to infants by their mothers (daily non-supervised group, n=70). In Group 3, iron was also given daily but by local staff (daily supervised group, n=67) and in Group 4, iron was given once per week by local staff (weekly supervised group, n=65). Iron status and growth were measured at baseline and three months later (T3) in all groups and again six months after baseline (T6) in groups 3 and 4. **Results:** At T3, hemoglobin concentration (Hb) improved in all groups but Hb changes were significantly higher in group 2 (21.6 ± 12.3 g/L) and in group 3 (15.4 ± 13.3 g/L) than in group 1 (8.0 ± 11.1g/L) (p<0.0001). Hb change in group 4 (11.2 ± 10.2 g/L) was not different from group 1 and group 3 but lower than in group 2. Between T3 and T6, Hb improved in both groups 3 and 4. Hb changes from baseline to T6 were not different between groups 3 (22.0 ± 12.1 g/L) and 4 (20.0 ± 10.2 g/L) and of similar magnitude than Hb changes from T0 to T3 in group 2 (21.6 ± 12.3 g/L). At baseline, prevalence of anemia was 82.6 %. By T3, anemia prevalence was decreased to 8.6 % in group 2 and to 50.0% in group 1. In group 3 anemia decreased from 85.1 % at T0 to 17.9% at T3, and 0% at T6. In group 4 anemia decreased respectively from 83.1% to 41.5 % and to 7.7%. No treatment showed any effect on growth. **Conclusion**: Both daily and weekly iron supplementation were effective to reduce iron deficiency anemia in Vietnamese infants over the total study period of 6 months. However, after 3 months of supplementation, daily supplementation was significantly more efficient than weekly supplementation. These results suggest that daily iron supplementation must be given to infants, at a period where adequate iron supply is essential to allow normal global development, at least for a period of three months which can be followed by a period of weekly supplementation. The higher increased of hemoglobin concentration in infants supplemented by their mothers suggest that three month-daily-iron supplementation is an effective strategy to control iron deficiency anemia in Vietnamese infants.

27 EFFECTS OF DAILY VERSUS WEEKLY IRON/FOLATE SUPPLEMENTATION TO PREGNANT WOMEN, RURAL NORTHEAST THAILAND AND FOLLOW-UP 4-6 MONTHS OLD INFANTS.

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Daily iron supplementation has been recommended as the key strategy for pregnant women both in developed and developing countries. Poor compliance led to attempt to identify alternative intervention to improve effectiveness of program. Weekly iron supplementation was proposed and tested in pregnant women in several settings. In Thailand, a study was conducted in rural northeastern villages, inclusive of 379 pregnant women, who completed the study. Women were randomly allocated to receive one of the three regimens: daily (60 mg Fe + 0.25 mg folic acid/day), 120 or 180 mg Fe + 3.5 mg folic acid /week). Iron plus folic acid were given to pregnant women, starting at 15 ± 2 weeks of gestation until 34 ± 2 weeks of gestation. Results showed that hemoglobin and ferritin in weekly groups were not statistically different from the daily group, both gross effects and after controlling for initial status, and age (repeated measures ANOVA). The reduction in prevalence was only observed in the daily (27.7 vs 22.7%) and the high weekly group (25.2 vs 22.5%). The prevalence was increased in the low weekly group (18.9 vs 31.5%). There was no subject whose hemoglobin fell below 9 g/dl in any groups at post measurement. Women having abnormal hemoglobin also responded similarly, and no adverse consequences were observed during the study. Infants from these mothers were followed at 4-6 months old and prevalence of anemia was found to be as high as 30%, especially the low weekly dose was the highest.

28 TREATMENT OF IRON DEFICIENCY IN GOITROUS CHILDREN IMPROVES THE EFFICACY OF IODIZED SALT.

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Background In many developing countries, children are at high risk for both goiter and iron-deficiency anemia. Because iron deficiency adversely effects thyroid metabolism, a high prevalence of iron deficiency may reduce response to iodine supplementation in areas of endemic goiter. Our recent studies in Côte d'Ivoire have shown that the therapeutic response to oral iodized oil is impaired in goitrous children with iron-deficiency anemia (IDA), compared to iron-sufficient, non-anemic children. The aim of this study was to determine if treatment of iron deficiency in goitrous children could improve the efficacy of iodized salt.

Methods We conducted a prospective randomized double-blind placebo-controlled trial comparing iodine and iron supplementation to iodine supplementation and placebo in 5-14 yr-old children in western Côte d'Ivoire. Goitrous, iron-deficient children (n=166) consuming iodized salt (10-30ppm at the household level) were assigned to receive either iron supplementation (60 mg iron/day, 4 days/week) or placebo for 16 weeks. The children were followed for 20 weeks with measurements of urinary iodine (UI), thyroid stimulating hormone (TSH), thyroxine (T_4), thyroid gland volume using ultrasound, hemoglobin (Hb), whole-blood zinc protoporphyrin (ZnPP), serum ferritin (SF) and serum transferrin receptor (TfR).

Findings Iron supplementation significantly increased mean Hb (SD) from 110(10) g/L at baseline to 124(9) g/L at 20 weeks (p<0.05), and decreased the anemia prevalence from 83% to 33%. The children treated with iron had a significantly greater reduction in thyroid size and goiter prevalence at 20 weeks compared to placebo. At 20 weeks, mean (SD)% decrease in thyroid volume compared to baseline in the iron and placebo groups was –22.8 (10.7)% and –12.7 (10.1)% (p<0.001). The goiter prevalence was 43% in the iron-treated group and 60% in the placebo group at 20 weeks (p<0.05).

Interpretation Iron supplementation improved the efficacy of iodized salt and iodized oil in goitrous children with iron deficiency. A high prevalence of iron deficiency may reduce response to iodine prophylaxis in areas of endemic goiter.

29 HUMAN MILK AS A SOURCE OF ASCORBIC ACID TO IMPROVE IRON BIOAVAILABILITY FROM COMPLEMENTARY FOODS.

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Background: Traditional complementary foods in West Africa consist mainly of cereals, tubers and other traditional staple foods. These foods are high in phytic acid, a strong inhibitor of iron absorption and contain no ascorbic acid, a potent enhancer of iron absorption. Traditionally, fruits or vegetables rich in ascorbic acid are not included in the diet during early life in West Africa and an alternative source of ascorbic acid, human milk, was therefore evaluated in this study. **Aims:** To evaluate human milk as a source of ascorbic acid in the diet of weanling infants in Côte d'Ivoire. **Study design:** Human milk ascorbic acid was analyzed in spot samples from African women and the effect of ascorbic acid supplementation and dietary interventions on human milk ascorbic acid was evaluated. Data on iron status and dietary intake (3-day weighed records) were collected from children (6-18 months old) in Abidjan. **Results:** Mean ascorbic acid in human milk was 33 mg/kg (range 7-79 mg/kg; n=171). Supplementation with 1000 mg ascorbic acid/day or 100 mg ascorbic acid/day during 10 days increased mean milk ascorbic acid from 18 to 60 mg/kg ($p<0.001$; n=22) and from 15 to 34 mg/kg ($p<0.001$; n=12). Consumption of 3 or 5 servings of fresh orange juice per week (about 100 mg ascorbic acid/serving) during 6-8 weeks increased human milk ascorbic acid significantly ($p<0.001$) from 15 to 37 mg/kg (n=15) and from 19 to 46 mg/kg (n=13), respectively. All 51 children were anemic; 86 % were iron deficient based on low ferritin (<12 µg/l) and 82 % had elevated transferrin receptor concentration (>8.5 mg/l). Average major meal content of ascorbic acid and iron was 0.7 mg (range 0-7 mg) and 0.6 mg (range 0.1-2.2 mg) respectively. Almost all (98%) children were breast-fed at least once a day within 30 minutes of a major meal. With the addition of human milk, the mean content of ascorbic acid increased to 2.2 mg and the molar ratio ascorbic acid:iron was > 1 in 64% of meals after intake of human milk. **Conclusions:** Human milk can be an important source of ascorbic acid in the diet of young children. The results from this study highlight the importance of encouraging regular consumption of ascorbic acid rich fruit by lactating mothers to ensure adequate ascorbic acid in human milk and the importance of promoting breast-feeding shortly after intake of solid/semi-solid meals.

30 IRON BIOAVAILABILITY FROM IRON FORTIFIED FISH SAUCE AND SOY SAUCE.

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Background: Iron (Fe) fortification of foods is a cost-effective and sustainable approach to combat Fe deficiency anemia. Fish sauce and soy sauce have been suggested as suitable vehicles for Fe fortification programs in China and Southeast Asia since these condiments are regularly consumed by a large proportion of the population. **Aim:** The aims of these studies were a) to measure Fe absorption from a test meal based on rice and vegetables served with $FeSO_4$ or NaFeEDTA fortified fish sauce or soy sauce (studies 1 and 4), b) to evaluate the effect of fish sauce or soy sauce *per se* on Fe absorption (studies 2 and 5) and c) to compare NaFeEDTA fortified fish sauce and soy sauce as fortification vehicles (study 3). **Method**: Fe absorption was based on the erythrocyte incorporation of stable isotopes (^{57}Fe and ^{58}Fe) 14 days after intake of labeled test meals. Fifty apparently health female students (age 19-29) were recruited in Zürich and randomly assigned to the separate studies (10 subjects/study). Each test meal contained 5 mg added Fe, including 4 mg labeled NaFeEDTA or $FeSO_4$. All test meals were based on 50 g rice (dry weight). In Studies 1 and 4, the rice was served with 25 g mixed vegetables. Ten g fish sauce or soy sauce were added when applicable. **Results**: Geometric mean Fe absorption from the test meal based on rice and vegetables served with 10 g NaFeEDTA fortified fish sauce providing 5 mg Fe was 3.3 %, compared to 3.1 % when the sauce was fortified with ferrous sulfate. When the rice and vegetable meal was served with 10 g NaFeEDTA fortified soy sauce mean Fe absorption was 6.2 % compared to 5.6 % from soy sauce fortified with ferrous sulfate. In neither of these two studies did NaFeEDTA significantly enhance Fe absorption compared to ferrous sulfate. When a meal based on rice alone was served with 10 g fish sauce mean Fe absorption was 6.7 %, which was not statistically significant different to the 8.9 % Fe absorption observed from the rice meal served with soy sauce. Both sauces inhibited Fe absorption when added to rice, although the decrease in Fe absorption was statistically significant only for soy sauce; mean Fe absorption from the ferrous sulfate fortified rice meal decreased from 11.6 % to 9.4 % after the addition of 10 g fish sauce and from 8.5 % to 6.0 % after the addition of 10 g soy sauce. **Conclusion**: Fe absorption was similar from the two Fe fortificants evaluated in this study. However, NaFeEDTA can be added to fish sauce and soy sauce without causing sensory problems while ferrous sulfate causes unacceptable precipitation. Fe absorption from rice based meals served with NaFeEDTA fortified fish sauce or soy sauce is nutritionally relevant and these condiments can be recommended as useful fortification vehicles.

31 THE EFFECT OF A MULTIPLE MICRONUTRIENT FORTIFIED FRUIT DRINK WITH AND WITHOUT ANTIHELMENTIC THERAPY ON GROWTH, FITNESS AND MENTAL ABILITY OF FILIPINO SCHOOL CHILDREN.

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The effect of a multiple micronutrient-fortified drink with and without antihelmintic treatment on growth, fitness and mental ability was studied on 808 subjects aged 6-12y in Balete, Batangas, Philippines. The study was a double-masked, randomized, placebo-controlled trial in 4 rural schools. Anthropometric, biochemical, parasitological, fitness and cognitive measurements were assessed at baseline and after 16 wks of intervention. At baseline, 52% were anemic at Hb<12 g/dl, 21% were moderately/severely anemic at Hb<11g/dl; 90% and 37% were iodine deficient (ID) at urinary iodine (UI) concentrations of <=100 µg/l and <=20 µg/l, respectively. The effect of fortification on fitness was seen only among those who were moderately ID (UI≥20-≤50 µg/L) and mildly anemic (Hb≥11-<12 g/dl) subjects. In this subgroup, the mean change in the fitness index scores from baseline to post-intervention was higher in the fortified than in the unfortified groups ($\bar{x}_{fort}$=5.00 vs $\bar{x}_{unfort}$=0.64, p=0.0492). The fortified drink also had a significant effect in improving the mental ability of mildly ID (UI>50-≤100 µg/L) and moderately/severely anemic (Hb<11 g/dl) children. The mean change from baseline to post-intervention in verbal ability ($\bar{x}_{fort}$=1.05 vs $\bar{x}_{unfort}$=-1.30, p=0.0218), non-verbal ability ($\bar{x}_{fort}$=2.08 vs $\bar{x}_{unfort}$=-0.18, p=0.0246) and total cognitive ($\bar{x}_{fort}$=5.29 vs $\bar{x}_{unfort}$=0.42, p=0.0234) scores in this subgroup was significantly higher among the fortified groups. Fortification had no effect on growth due to the short intervention period. The effect of deworming on growth was evident only among subjects who were severely ID (UI<20 µg/L). Mean change from baseline to post-intervention in weight-for-age ($\bar{x}_{albendazole}$=0.11 vs $\bar{x}_{placebo}$=0.07, p=0.0407) and weight-for-height ($\bar{x}_{albendazole}$=0.12 vs $\bar{x}_{placebo}$=-0.03, p=0.0052) z-scores was significantly higher in the albendazole than in the placebo groups. Deworming had no effect on fitness and mental ability of the subjects. This study showed that consumption of a multiple-micronutrient fortified beverage for 16 weeks had a beneficial effect on the physical fitness of moderately ID and mildly anemic children and mental ability of mildly ID and moderately/severely anemic children, and that deworming resulted in an improvement of weight-for-age and weight-for-height z-scores of severely ID children.

32 HOW MUCH AND HOW FAST WILL IRON STATUS BE CHANGED IN A POPULATION WHEN FORTIFYING A DIET OR WHEN MODIFYING ITS COMPOSITION TO INCREASE IRON BIOAVAILABILITY ?

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Aims: Prediction of effects expected of iron intervention programs.

Method: Based on several studies on iron absorption from the whole diet in women and men, it has been possible to derive an exponential general equation describing the relationship between iron absorption (intake * bioavailability), iron requirements and iron stores (positive or "negative"). This equation can be used to used to describe stationary states (iron stores etc) under different conditions. By integrating the equation, the rate of change of iron status (iron stores or circulating hemoglobin deficits) can be calculated with no further assumptions.

Results: When increasing dietary iron absorption by iron fortification or by modification of the composition of the diet e.g. by increasing intake of meat, fish, ascorbic acid or decreasing intake of phytate or iron-binding polyphenols, the rate of change of iron status will always be the same with a 90% increase within 1 year. The absolute change over time of iron status can also be estimated from known changes of iron losses and iron absorption.

Conclusions: The new methods developed are important tools in prediction of effects epected of iron intervention programs, in selection of design and in interpretation of results.

33 **IMPACT OF IRON FORTIFIED MILK IN INFANTS: EVALUATION OF EFFECTIVENESS.** **Eva Hertrampf, Manuel Olivares, Fernando Pizarro, Tomás Walter. Institute of Nutrition and Food Technology (INTA), Universidad de Chile, Santiago, Chile.**

Background: Since 1999, the Ministry of Health provides the 70% of Chilean infants with 2 kg/month of a powdered full fat milk fortified with iron (10mg/100g as ferrous sulphate), zinc (5 mg/100g), copper (0.05mg/100g) and ascorbic acid (70mg/100g) from birth to 18 mo of age free of cost, through the National Supplementary Food Program. This milk is consumed by the lactating women until their infants are spontaneously weaned (60% of Chilean infants are weaned at 6 mo of age) **Aims:** A study was conducted to evaluate the effectiveness of this milk on IDA prevention under the conditions of normal distribution in the Primary Care Health Clinics (PCHC) previous (baseline) and one year after the introduction of the fortified milk . **Methods:** All infants between 12 to 18 mo who attended to receive vaccines at one PCHC in Santiago were evaluated *before* (June 1999, n=128) and *after fortification* (June 2000, n=125). Hemoglobin (Hemocue), FEP (Hematofluorimeter, AVIV) and serum ferritin (ELISA) were measured from a capillary sample. **Results:** Infants in both groups were exclusively breast-fed for 5 months approximately (4.5±3.3 and 5.6±3.3 mo). At baseline, anemia (Hb<11 g/dL) was present in the 27.3% of infants, after fortification the prevalence decreased to 8.8% (p<.0001). The corresponding figures for FEP (>100ug/dL RBC) were 67 and 32.1% (p<.0001) and for serum ferritin (<10 ug/L) 28.6 and 23.2% respectively (NS). **Conclusions:** The delivery of a fortified powdered full fat cow´s milk through the National Supplementary Food Program in Chile is effective in preventing IDA and iron deficient erythropoiesis, however there is not an impact on iron stores.

34 **THE CULTURAL ECOLOGY OF IRON INTAKE IN NORTHERN KENYA: EXPLORING DIETARY MODIFICATION AS A SUSTAINABLE APPROACH TO PREVENTING IRON DEFICIENCY.** **Bettina Shell-Duncan, Thomas McDade. Department of Anthropology and International Health Program, University of Washington, Seattle, WA, USA; Department of Anthropology, Northwestern University, Evanston IL, USA.**

Background: Iron deficiency (ID) affects an estimated 49% of school-aged children in Africa, and bears serious costs including impaired learning and school performance, growth faltering, and increased risk of infectious morbidity. As a first step toward the initiation of a large-scale program for the prevention of ID among school-aged children, a nutrition baseline survey was conducted in northern Kenya. **Aims:** The objectives were to determine the prevalence of ID among school-aged children as related to nutritional status, parasitic infection, dietary habits and proscriptions, and sociodemographic factors. The information is intended to identify determinants of ID and highlight avenues for intervention. **Methods:** In a 30-cluster random sampling design, 314 children were selected from two rural dryland settlements. A pre-tested questionnaire was used to obtain sociodemographic and 24-hour dietary recall data from the primary caretaker of each subject. In addition, qualitative data on food beliefs and taboos were obtained. After obtaining anthropomentrics from each pediatric subject, capillary blood from a finger stick was used to determine hemoglobin level, and to prepare a thick and thin smear for evaluating hemoglobinopathies and parasitemia. Remaining blood was collected in capillary tubes and filter paper for later determination of zinc protoporphyrin:heme ratio (ZPP:H) and C-reactive protein (CRP). **Results:** ID was determined by subnormal hemoglobin and/or elevated ZPP:H in the absence of elevated CRP, which indicates current or recent infection that may independently alter biochemical indices of iron status. Overall, 33% of children were diagnosed with ID, which is largely attributable to low dietary iron. 24-hour recall data reveal a low iron diet (predominantly maizemeal and tea) with a high content of iron absorption inhibitors; heme iron (meat and blood) was consumed by only 14% of subjects. Socio-demographic analysis reveals that, after controlling for economic status, girls have a 2.2 x higher risk of ID in comparison to boys. This parallels culturally defined gender-based prescriptions for child feeding: girls are believed to benefit from "soft foods", including rice, maize porridge and tea, whereas boys benefit from "hard foods", including meat, blood and beans. As a result, in households economically able to purchase iron-rich foods, these foods are being preferentially fed to boys. **Conclusions:** Economic development may result in improved iron status for boys, but will be unlikely to benefit girls in the absence of a dietary modification intervention. A modification of culturally acceptable "soft foods" to include iron-rich foods may provide a sustainable approach to controlling and preventing ID.

35 **REGULAR CONSUMPTION OF NaFeEDTA FORTIFIED FISH SAUCE IMPROVES HEMOGLOBIN IN ANEMIC VIETNAMESE WOMEN**

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Background: Fish-sauce, consumed daily by a large proportion of the Vietnamese population, is a potentially useful food vehicle for iron fortification. **Aim of the study:** To evaluate the efficacy of NaFeEDTA fortified fish-sauce to improve iron status of adult women. **Method:** A randomized, double blind controlled trial in 152 anemic (hemoglobin 80-119 g/L) women working in garment factories in the Red River Delta of Vietnam. All women were served a meal based on noodles or rice, six days per week under strict supervision, with 10ml fish-sauce containing either 10mg of iron as NaFeEDTA (group 1) or no added iron (group 2). Iron status (hemoglobin, ferritin and transferrin receptor) was evaluated at baseline and after 110 days (T3) and 200 days of intervention (T6). **Results:** 130 women completed the study; 62 in group 1 and 68 in group 2. The women consumed on average 148 meals during the intervention (range 121-163). Hemoglobin concentration increased in group 1 from 110.5±8.0 g/L (X±SD) at baseline to 111.9±8.8 g/L (p=0.16) at T3 and to 116.4±8.8 g/L at T6 (p<0.0001). Hemoglobin decreased in group 2 from 110.3±8.9 g/L (baseline) to 106.1±10.2 g/L (p<0.0001) at T3 and to 106.9±11.0 g/L at T6 (p=0.003). At T3 and T6, the hemoglobin concentration was significantly higher (p<0.0001, repeated measures Anova) in group 1 as compared with group 2. Changes in hemoglobin as compared with baseline were significantly different between the two groups at T3 (1.4±7.9 g/L in group 1 versus –4.19±7.2 g/L in group 2, p<0.0001) and T6 (5.9±10.4 g/L versus –3.3±8.8 g/L, p<0.0001). By the end of the study, the prevalence of anemia had decreased 33.9% in group 1 and 10.3% in group 2. Ferritin and transferrin receptor data will be presented in the poster. **Conclusion:** Regular consumption of iron fortified fish-sauce (10mg iron as NaFeEDTA/10ml fish-sauce) improved hemoglobin concentration significantly and decreased the prevalence of anemia in Vietnamese women significantly during the 6 month intervention. Iron fortification of fish sauce is a promising strategy to combat iron deficiency anemia in Vietnam.

36 **IRON ABSORPTION FROM RICE/RICE BASED MEAL FORTIFIED WITH DIFFERENT IRON FORTIFICANTS.** **Trinidad P. Trinidad, Ph.D., Divinagracia H. Valdez, Aida C. Mallillin, Faridah C. Askali, Allan Francis P. Dara-ug, Mario V. Capanzana, Ph.D. Food and Nutrition Research Institute, Department of Science and Technology, Bicutan, Tagig, Metro Manila 1631 Philippines.**

Iron (Fe) absorption from rice fortified with different iron (Fe II) fortificants, Fe sulfate, NaFeEDTA, Fe fumarate and Fe bisglycinate was determined using *in vitro* enzymatic digestion simulating conditions in the small intestine and *in vivo* using radioisotope techniques. I*n vitro* results showed that the percent Fe release from NaFeEDTA (15.7±0.9) and Fe sulfate fortified rice (13.2±1.5) was significantly greater than with Fe fumarate (6.4±0.6; P<0.05) and Fe bisglycinate (3.3±0.8; P<0.05). Fe absorption *in vivo* was investigated for the treatment with the highest Fe release in ten borderline Fe-deficient subjects, Fe sulfate and NaFeEDTA fortified rice with and without fish and vegetables. Fe absorbed (mg) from NaFeEDTA fortified rice (0.44±0.11) was significantly greater than Fe sulfate (0.22±0.05; P<0.05) and the unfortified rice (0.17±0.02; P<0.05), while Fe absorption from Fe sulfate fortified rice did not differ significantly with unfortified rice. Fe absorbed (mg) from a meal consisting of Fe-fortified rice, fish and vegetables was significantly greater from NaFeEDTA (0.88±0.24) and Fe sulfate (0.67±0.10) than the unfortified rice (0.41±0.08; P<0.05). The Fe absorbed from NaFeEDTA and Fe sulfate fortified rice with fish and vegetables did not differ significantly. For all treatments, Fe absorption from rice with fish and vegetables were significantly greater than Fe absorption from rice alone. This study concludes that both NaFeEDTA and Fe sulfate are effective Fe fortificants of rice. The binder used in the study may have a significant role in the release of Fe from Fe-fortified rice for absorption. Further studies on the use of other binders to maximize Fe release and minimize Fe loss during cooking should be done to improve Fe absorption from the fortified rice/rice-fish-vegetable meal. Results from this study can be used as a basis for food Fe fortification program as well as in the establishment of recommended dietary allowances for Fe among Filipinos

37 **THE EFFECT OF PROVIDING SALT FORTIFIED WITH IRON AND IODINE ON THE HEMOGLOBIN AND PRODUCTIVITY OF TEA PLUCKERS.**

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AIM : To test the impact of Double Fortified Salt on increasing the Hemoglobin levels and the productivity in tea pluckers.

METHODS : A double blind randomised placibo control study was conducted on 793 tea pluckers. The subjects in the experimental households (n=408) received Double Fortified Salt - salt fortified with iron and iodine and the subjects (n=385) in the control households received the common unfortified salt. The finger prick blood analysis for hemoglobin by cyanamet hemoglobin method was done for a period of one year. There were three measurements - initial measurement before the start of the trial, middle measurement after six months and final measurement after one year. Validation was done for the 10% of the population. Deworming was done for 50% of the population in the experimental and control areas. The productivity data was also analysed for 450 tea pluckers. Two criterion analysis of variance was done for productivity data. The two criteria for analysis of variance were (1) Experimental and Control groups and (2) Deworming and Non-deworming.

RESULTS : At the end of one year period of clinical trials, it was found that the average hemoglobin had increased from 8.87 gms/dl to 10.35 gms/dl and the corresponding plucking average i.e. the quantities of tea leaves plucked per day per person had increased from 24.84 kgs to 26.15 kgs in the dewormed experimental group.

The experimental dewormed group have plucked 1.1 kgs of tea leaves more per day compared to the control dewormed group at the end of the trial. If this data can be extrapolated for 1000 workers, then it would mean that these 1000 workers could have plucked 1000 x 1.1 kgs of extra tea leaves per day. This would mean 27.5 tons of extra tea leaves plucked per month or 330 tons of extra tea leaves plucked per annum.

CONCLUSIONS : The study shows that an insignificant sum of money spent on eliminating micronutrient deficiencies could go a long way in phenominally improving the productivity of industries.

38 **RANDOMIZED CONTROLLED TRIAL OF MICROENCAPSULATED FERROUS FUMARATE 'SPRINKLES' AND FERROUS SULFATE DROPS, FOR TREATMENT AND PREVENTION OF ANEMIA IN GHANAIAN INFANTS .**

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Background. The standard treatment of anemia in infants is ferrous sulfate (DROPS) given 3-times daily. Adherence to long-term use of DROPS is often poor. Thus we developed a novel delivery system with microencapsulated ferrous fumarate and ascorbic acid (SPRINKLES) that can be sprinkled onto complimentary foods. **Aim.** To compare the use of SPRINKLES (± vitamin A) vs DROPS in the treatment and prevention of anemia in infants. **Methods.** A randomized controlled trial in 2 consecutive phases: **(i) Treatment Phase:** 557 anemic children (age 6-18 mo; hemoglobin (Hb) 70-99 g/L) in rural Ghana were studied. One group received daily SPRINKLES (80 mg Fe); and the control group DROPS 3-times daily (40 mg Fe, total) for 2 months. In both studies, Hb and serum ferritin (ferr) values were measured at baseline and end. **(ii) Prevention Phase:** Infants who recovered from anemia in the initial phase of the study were eligible. 324 children (age 15.6±4.5 mo; Hb≥100g/L, ferr≥12μg/L) were studied for 6 months with daily intervention. Four groups included: (1) DROPS, 12.5 mg Fe; (2) PLACEBO, no Fe; (3) SPRINKLES, 40 mg Fe; and (4) SPRINKLES with vitamin A, 40 mg Fe + 2000 IU RE. **Results. (i)** Successful treatment of anemia (Hb>100g/L) occurred in 58% of SPRINKLES group, and in 56% of the DROPS group ($p=0.51$). Ferr levels increased in each group from baseline to end ($p<0.001$). **(ii)** Among the 4 groups, there were no significant differences in mean Hb values (112.2±14.7g/L, $p=0.70$) or ferr (median=62.8μg/L) from baseline to end. During the trial, 82.4% maintained their non-anemic status. **Conclusions.** Use of DROPS or SPRINKLES resulted in a similar rate of successful treatment of anemia. In previously treated infants, there is no need for further intervention to prevent anemia at least for 6 months. Sprinkles were well accepted without side effects in both phases. **Implications.** Although beyond the scope of this study, improved adherence and ease of use may favor the use of SPRINKLES to deliver iron for intervention programs in developing countries. Supported by USAID's OMNI Research Program through the HNI of ILSI.