Prevention of Micronutrient Deficiencies: Tools for Policymakers and Public Health Workers

Christopher P. Howson, Eileen T. Kennedy, and Abraham Horwitz, Editors; Committee on Micronutrient Deficiencies, Institute of Medicine

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Tools for Policymakers and Public Health Workers

Committee on Micronutrient Deficiencies
Board on International Health
Food and Nutrition Board
INSTITUTE OF MEDICINE

Christopher P. Howson, Eileen T. Kennedy, and Abraham Horwitz, *Editors*

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DEDICATED TO

Abraham Horwitz, M.D.

For his extraordinary commitment to this report and to the ideal of health for all.

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Summary

Millions of people suffer and many die from lack of minute traces of nutrients. Methods of prevention are cheap and simple. Their universal application could yield health and economic benefits comparable to those achieved by smallpox eradication.
— Dr. V. Ramalingaswami, Chair, LTNDP Task Force on Health Research and Development, Ending Hidden Hunger Conference, Montreal, Canada, October, 1991

Micronutrient malnutrition affects approximately 2 billion people worldwide. The adverse sequelae of micronutrient deficiencies are profound and include premature death, poor health, blindness, growth stunting, mental retardation, learning disabilities, and low work capacity. Worldwide attention first focused on the massive problem of micronutrient malnutrition in the mid- to late 1980s. A pivotal event that fostered this attention was a U.S. Agency for International Development (USAID) -funded randomized trial of vitamin A supplementation in Aceh Province, Indonesia, conducted by Dr. Alfred Sommer and colleagues. In this study, vitamin A-supplemented preschoolers were observed to have a 34 percent reduction in mortality. Thus, while vitamin A deficiency had long been associated with blindness, the Aceh research clearly demonstrated a link between vitamin A deficiency and mortality.[1] These findings prompted the United Nations Subcommittee on Nutrition to issue a statement in 1992 indicating that control of vitamin A deficiency might be an important way to reduce mortality in young children.[2]

PROJECT CHARGE

The Aceh project was one of a series of interventions implemented in the 1980s that was aimed at alleviating the "hidden hunger" of micronutrient

[1] Sommer, A., et al. 1986. Impact of Vitamin A Supplementation on Childhood Mortality. The Aceh Study Group. *Lancet* 1 (8491):1169-1173.

[2] United Nations. 1992. Administrative Coordinating Committee, Subcommittee on Nutrition. Second Report on the World Nutrition Situation. Vol. 1, October 1992, p. 40. Geneva: United Nations.

malnutrition. Although some of these interventions have been successful, a majority have not. Nevertheless, there had been no systematic examination of the reasons for these successes or constraints in program outcome. Recognizing this, the Office of Health and Nutrition of USAID decided that there was a need to bring together research scientists and project implementers to examine past approaches that had—or had not—been successful and to identify the elements of success or constraint. USAID requested that the Institute of Medicine's Board on International Health oversee this activity and draft a report directed to those funding U.S. and international programs to alleviate micronutrient malnutrition. Given this audience, the report does not offer recommendations on how to alleviate specific micronutrient deficiencies—such recommendations are already available through the publications of diverse organizations, including USAID, the Micronutrient Initiative, the World Bank, the United Nations Childrens' Fund (UNICEF), and the World Health Organization (WHO). Rather, this report provides a conceptual framework based on past experience that will allow funders to tailor programs to existing regional/country capabilities and to incorporate within these programs the capacity to address multiple strategies (i.e., supplementation/fortification/food-based appro-aches/ public health measures) and multiple micronutrient deficiencies.

To respond to USAID's request, the Board on International Health—in consultation with the Food and Nutrition Board—constituted an expert committee of eleven members with broad expertise related to micronutrient nutrition, diet, and health, especially as these relate to iron, vitamin A, and iodine, and to the conduct and evaluation of global micronutrient deficiency prevention programs. The committee focused on iron, vitamin A, and iodine because they believed there was sufficient literature and program experience on each to warrant review. Although the project concentrates on these three micronutrients, it is hoped that similar reviews of other key micronutrients—for example, zinc, folate, and vitamin B12—will be conducted as literature and experience accumulate. In addition, while the background papers focus on interventions conducted in developing countries, the committee broadened its conceptual framework and recommendations to encompass at-risk populations in industrialized countries as well.

The eight-month project was conducted in two phases. Phase 1 featured a two-day workshop to evaluate successful approaches to the prevention of micronutrient malnutrition and to identify the elements that had led to this success. Workshop participants included committee members and additional experts with research and program expertise related to the committee's task. In planning the workshop, the committee recognized that while there is an array of potential alternative strategies to deal with micronutrient malnutrition, it is unlikely that any one intervention, by itself, will solve all the micronutrient deficiencies in a given region or country. Thus, the mix of scientists and project implementers invited to the workshop was designed to help ensure identification of the optimal combinations

of interventions most likely to be successful in a selected context. The range of participants also allowed for complementarities in treating micronutrient deficiencies to be identified.

Three background papers—evaluating iron, vitamin A, and iodine deficiency interventions, respectively—were commissioned in advance of the meeting. These provided a basis for much of the workshop discussion. The papers were updated following the workshop on the basis of recommendations from participants.

This report of the committee provides the basis for Phase 2 of the project, which will involve convening representatives of key U.S. and international organizations with a programmatic interest in combating micronutrient deficiencies. Participants will discuss the implications of the report's findings and recommendations for future policy and action. The meeting will be held in early 1998.

ORGANIZATION OF THE REPORT

The report contains five chapters and one appendix. Chapter 1 summarizes the findings and recommendations of the workshop. Chapter 2 provides a synthesis of the discussions of the two working groups and the subsequent plenary discussion. Chapters 3 through 5 present the three background papers on iron, vitamin A, and iodine. The Appendix contains the workshop agenda.

Chapters 1 and 2 focus on overarching themes that emerged from the workshop proceedings. In these chapters, the committee has attempted to provide a framework for planning intervention programs that integrates three micronutrients and provides matrices for assigning priorities to interventions in different contexts. The committee offers these matrices as guidelines only, recognizing that there may be circumstances in which unique personalities, opportunities, or barriers exist that may lead countries to deviate from the priorities in the matrix. The committee believes, however, that the matrices offer a useful starting point for planners and donor agencies.

Readers interested in information on the specific micronutrients—iron, vitamin A, and iodine—should refer to the background papers presented in Chapters 3 to 5.

FINDINGS AND RECOMMENDATIONS

Findings

- **Deficiencies of iron, vitamin A, and iodine are still highly prevalent in the world. Approximately 2 billion people—or one-third of the human race—are affected and at increased risk of death, disease, or disability as a result.**

These deficiencies disproportionately affect the groups most vulnerable to nutrient deficiency: women of childbearing age, pregnant women, lactating mothers, and children under 5 years of age.

The consequences of iron, vitamin A, and iodine deficiencies are severe, both with respect to health and to the damaged human capital and national economic development they impose, particularly in developing countries. *Iron deficiency* (ID) affects over one billion people, particularly children and women. If uncorrected, iron deficiency leads to anemia, reduced work capacity, diminished learning ability, increased susceptibility to infection, and greater risk of maternal and childhood mortality. *Vitamin A deficiency*, defined by characteristic eye signs, has been identified as a public health problem in over 40 developing countries. The consequences of vitamin A deficiency (VAD) include increased risk of severe morbidity, mortality in children, and blindness. *Iodine deficiency disorder* (IDD) exists in most parts of the world, primarily because of low intake of iodine in the diet. The consequences of IDD include goiter, reduced mental function, increased rates of stillbirths and abortions, and infant deaths.

- **The nutrition status of all populations is in flux. Groups are in continuous movement along a continuum of nutritional risk, extending from a situation of severe micronutrient malnutrition, through a wide spectrum of presumed nutrient adequacy, to one of nutrient overload and toxicity at the upper end.**

The goal of micronutrient interventions should be to move at-risk groups within populations along a continuum from a state of public health risk or crisis, which occurs when deficiencies and their health consequences are widespread, to states of nutrient sufficiency and health.

- **There exists a "toolchest" of effective interventions against micronutrient malnutrition. These interventions include supplementation, food fortification, dietary diversification, and public health measures such as parasite and diarrheal disease control.**

Availability of the toolchest alone, however, does not ensure programmatic success. Review of past efforts indicates that many programs may have been designed or implemented without adequate attention to country circumstances or the context in which the intervention would be conducted. The "one size fits all" approach to identifying effective micronutrient interventions has not worked in the past, and it is unlikely to succeed in the future. Rather, successful programs meet the nutritional needs over time of at-risk groups within both resource constraints and the local cultural context. Review of successful past programs suggests that they were more likely than less effective interventions to have been tailored to local circumstances, matching the level of effort to the severity and prevalence of

deficiency, addressing the constellation of preventable causes of deficiency, and tailoring their operations to a country's capacity to implement and sustain the intervention.

- **Past interventions have focused on single micronutrients, thus missing opportunities to coordinate and leverage scarce human and financial resources across funding agencies and the programs they conduct.**

In addition, relatively few interventions have incorporated complementary public health control measures—for example, integrating dietary with supplementary measures or parasite control or the teaching of personal hygiene and sanitation practices—in their approaches to the alleviation of micronutrient malnutrition.

- **Review of past programs reveals an almost total lack of attention in program design and implementation to the systematic collection of data on costs linked to program components and effectiveness of different interventions.**

Such program monitoring is essential to providing information on appropriate ways to improve the efficiency of implementation and coverage of given strategies in different country settings.

The following recommendations were developed by the committee, based on the workshop deliberations and on the background papers presented in Chapters 3 to 5.

Recommendations

- **Successful interventions to date have incorporated knowledge of key factors—including the location (or clustering), severity, prevalence, and multiple causes of the deficiency(ies); level of country development; and the country's capacity to implement and sustain the intervention. Advance in-country analysis, coupled with timely, ongoing feedback and the flexibility to change programs as indicated, are essential to initially determine program targets, modify elements, and to remain efficient and effective in the long run.**

Program support from external donor agencies has been essential to the success of intervention programs to date, but such support—in order to be maximally effective in the future—must be better tailored to target country needs and capabilities than it has been in the past. Support should also be maintained for a sufficient and biologically plausible period of time to show success in achieving nutritional goals within the framework of the host country's development

plan. Availability of short-term, goal-oriented, program-specific external funding should not be the primary factor driving the country program.

- **Because deficiency of a single micronutrient seldom occurs in isolation, often existing in the context of deprivation and multiple micronutrient deficiencies, plans for sustained intervention should consider interventions to target multiple deficiencies to the degree appropriate and feasible. Interventions should incorporate all four strategies—supplementation, fortification, food-based approaches leading to dietary diversification, and complementary public health control measures—again, to the degree appropriate and feasible. Only the relative emphasis and time sequence for the four approaches should differ, by level of population risk, phase of intervention, and the micronutrients under consideration.**

Supplementation is the method of choice when therapeutic treatment is necessary—that is, to address severe micronutrient deficiency. Supplementation is also an appropriate tool for preventive programs as long as the distribution system can be maintained and those receiving the supplements continue to consume them. Supplementation has been shown to be highly cost-effective in achieving its nutritional goals and health impact. There is concern, however, that it may be more costly to maintain than either fortification or dietary diversification in the long term, although data to substantiate this concern are lacking. To date, most of the efforts to control vitamin A and iron deficiencies have focused on supplementation; comparatively few programs have also included fortification and dietary diversification components. Evidence on vitamin A replenishment from the Indonesia experience of the 1970s and the Tanzania experience of the 1980s suggests that a more comprehensive approach, designed to provide therapeutic treatment for those with frank deficiency along with the preventive strategies for the general population, may yield better results in the longer term.

Food fortification, with the exception of iodized salt, and *dietary diversification* are not appropriate as therapeutic measures, but can be successful as sustainable preventive strategies to control micronutrient malnutrition. Food fortification requires the active participation of the food industry. Dietary diversification and changes in meal composition require individuals, families, and communities to change eating behavior in their unique cultural context. Both strategies require more time than supplementation to achieve the same change in micronutrient status. For this reason, supplementation has been the preferred preventive and therapeutic strategy. Food fortification, however, has the potential to reach a larger number of consumers than supplementation, and therefore to have broader impact, as evidenced by experiences with iodized salt and sugar fortification with vitamin A in Latin America.

Except for iodine, *food-based approaches* are the most logical for integrating micronutrient control programs. Interactions are avoided between

potential concentrated-dose incompatibilities among supplements, such as solubility differences, susceptibility to oxidation, and competition for absorption. The situation with IDD control is different, because the deficit is not correctable simply by growing more or different food in the same iodine-depleted area. Furthermore, there is a proven, cost-effective IDD control intervention—universal iodization of salt—that should receive continued support, using oral iodine supplements to control the problem in limited, unyielding situations.

Combining of nutritional interventions with other *complementary public health measures* is frequently necessary to eliminate deficiency of a specific micronutrient. Successful examples include coupling deworming with iron supplementation to control anemia or enhancement of vitamin A status through diarrheal disease control.

In addition, experience suggests that incorporating *temporal combinations* into an intervention—that is, combining short-term with longer-term approaches—increases the likelihood of sustained public health benefit. One such example was the effective emergency use of iodinated oil in Bolivia in the late 1980s while USI was being institutionalized.

- **The long-term goal of intervention should be to shift emphasis away from supplementation toward a combination of food fortification—universal salt iodization (USI) or iron-fortified flour, for example—and dietary diversification, where appropriate and feasible.**

In other words, as populations move along the continuum of risk from a position of higher to one of lower risk, the relative mix of interventions should favor food, modeled after that presented in Table 1-1.

- **There are a number of widely held beliefs among designers and implementers of micronutrient interventions that have not been empirically tested and that require such testing.**

Two examples of such "conventional wisdom" include:

1. *The belief that social marketing and education of recipients are essential to empower them to make informed decisions and to willingly participate*. These elements are viewed by many as a necessary component of all successful, long-term intervention activities. With the exception of the Thailand ivy gourd initiative (see Chapter 4), however, there are few examples to support this contention. Research should, therefore, be directed toward confirming the Thailand ivy gourd experience in other regions of the world, particularly given the additional costs and complexities associated with incorporating social marketing and nutrition education in prevention or control programs.

TABLE 1-1 Preferred Initial Approaches to Prevention and Control of Iron, Vitamin A, and Iodine Deficiencies in Populations at Different Levels of Micronutrient Malnutrition

	Level IV			Level III			Level II			Level I		
Deficiency	Iron	Vit A	Iodine	Iron	Vit A	Iodine	Iron	Vit A	Iodine	Iron	Vit A	Iodine
Supplementation												
Targeted to vulnerable groups	—	++	++++	+++	+++	++	+++	++	+	++	+	+
Universal	++++	++++	—	++	+	—	—	—	—	—	—	—
Fortification												
Targeted foods	+	+++	—	—	—	—	—	—	—	—	—	—
Universal	—	—	+++	+	++	++++	+++	++	++++	+++	++	++++
Food-based approaches												
Nutrition education	+	++	+	++	+++	+	+++	++++	+	++++	++++	++
Food production	++	+++	n.a.	+	++	n.a.	—	+	n.a.	—	—	n.a.
Food-to-food	++++	++++	—	+++	+++	—	—	—	—	—	—	—
Public health control measures												
Immunization	++++	++++	—	++++	++++	—	++++	++++	—	++++	++++	—
Parasite control	+++	++	—	+++	++	—	—	—	—	—	—	—
HW/S	+++	—	—	+++	++	—	—	—	—	—	—	—
DD/ARI	+++	+++	—	+++	++	—	—	—	—	—	—	—
Personal sanitation/hygiene	++++	++++	—	++++	++++	—	++++	++++	—	++++	++++	—

NOTE: Level IV, populations with severe micronutrient malnutrition; Level III, populations with moderate to severe micronutrient malnutrition; Level II, populations with mild and widespread micronutrient malnutrition; Level I, populations with mild and clustered micronutrient malnutrition; ++++, very strong emphasis; +++, strong emphasis; ++, moderate emphasis; +, light emphasis; —, no emphasis; food-to-food fortification, mixing of staple foodstuffs—e.g., mango with gruel—at the household level to enrich nutrient content; n.a., not applicable; HW/S, healthy water and public sanitation; DD/ARI, control of diarrheal diseases and acute respiratory infections.

2. *The belief that community-level involvement is critical to high-coverage and sustainability of progress achieved by programs* (where progress refers to continued program support that is political and public, as well as financial). Again, there is little past experience to support this contention; thus, confirmation is warranted.

- **There is a critical need for information systems that will allow governments and international funders to plan, monitor, and evaluate processes and outcomes of micronutrient intervention programs. Such information systems are most effective when designed and included in interventions from the start.**

Key elements of program information systems include:

—An ability to monitor sentinel aspects of performance at low cost and refine process and output in a way that provides timely and relevant feedback at each decisionmaking level of the program.

—A capability to monitor dietary intakes and micronutrient status over time, as needed, to detect changes in these key outcomes and to determine the level and stability of a population's risk so that interventions can be responsive to changes in need.

—Application of standard methods of quality assurance and control that can facilitate comparison of performance within and across interventions and allow for more systematic evaluation of the elements and context of program successes and failures in the future. Standardization of methods can also make it easier to decide which trials are the more promising for expansion to fully operational levels.

—Guidance from experts in nutrition, population sciences, food science and technology, management, and economics to assure the inclusion of critical program elements to monitor and evaluate programs.

- **Data on the costs and effectiveness of interventions for the control of micronutrient deficiencies should be collected routinely as part of all interventions.**

The collection of data on cost-effectiveness through operations research can provide information on appropriate ways to improve efficiency of implementation and enhance effectiveness of selected strategies in different country environments.

- **Funders should increasingly engage governments and the private sector—for example, national food industries and food cooperatives—as partners**

in achieving sustainable improvements in the micronutrient content of diets.

Because continued economic and social deprivation in target populations constrain implementation of interventions and the sustainability of progress, funders should also engage organizations that seek to improve the socioeconomic status in populations suffering micronutrient malnutrition as partners. As socioeconomic conditions gradually improve in many developing societies, it is likely that the private food industry will increasingly influence the nature and nutritional adequacy of the diets in these populations. Initiating constructive working relationships and instilling a sense of responsibility within the food industry are likely to yield stronger and more committed partnerships in preventing micronutrient deficiencies in the future.

2

Key Elements in the Design and Implementation of Micronutrient Interventions

The 1991 Montreal Conference[1] focused worldwide attention on "Hidden Hunger." Not only were millions of individuals affected by deficiencies of vitamin A, iron, and iodine, but solutions to these micronutrient deficiencies were technologically possible. Since the 1991 conference, a number of donors have committed substantial financial resources to solving the problem of "hidden hunger." Other efforts, including the 1992 report of the International Committee on Nutrition,[2] have helped stimulate national efforts to analyze nutritional problems and the resources available for their solution. Less attention, however, has been devoted to understanding the key elements needed to implement and sustain a micronutrient intervention on a fully operational scale (e.g., national, regional), as opposed to a pilot project scale, at either the national or community level.

Experience to date has shown that "how" an intervention is implemented may be as important, or in some cases more important, than "what" is implemented. Some research has already been conducted on elements of successful nutrition interventions generally; in 1989, the USAID International Nutrition Planners Forum held a workshop in Seoul, South Korea, on "Elements of Successful Community Nutrition Programs."[3] Similarly, a World Bank-funded project entitled "Successful Nutrition Programs in Africa: What Makes Them Work?"[4] evaluated elements of effective nutrition interventions in the region.

[1] "Ending Hidden Hunger" UNICEF/WHO Conference, Montreal, Canada, October, 1991.

[2] International Conference on Nutrition, FAO/WHO, Rome, Italy, December 1992.

[3] International Nutrition Planners Forum Workshop, "Elements of Successful Community Nutrition Programs," Seoul, Republic of Korea, August, 1989.

[4] Kennedy, E. 1991. Nutrition Interventions in Africa: What Makes Them Work? World Bank Working Series in Population, Health, and Nutrition. Washington, D.C.

Correspondingly little work, however, has been done on the elements of effective micronutrient interventions. While the design and implementation elements of effective micronutrient interventions may be identical to macronutrient nutrition interventions in general, it is worth taking a systematic look at the factors that account for—or constrain—their effectiveness.

This chapter draws on the discussions of the two working groups in the 5–7 December 1996 workshop (see the Appendix for agenda). Working Group I was charged with evaluating past experience with approaches to the prevention or correction of micronutrient malnutrition. The approaches examined included food-based strategies such as dietary change and fortification, supplementation, and other public health measures, including parasite control and delayed umbilical cord ligation. Working Group II looked more broadly at the major elements of success and constraint in past programs.

This chapter first describes the importance of iron, vitamin A, and iodine to health. It then considers options for successful interventions based on the level of development of the target country. The costs of interventions are also briefly reviewed.

In drafting this summary, the committee has followed two general rules. First, while elements of past experiences may differ among the specific micronutrients, the committee paid special attention to successful examples of strategies incorporating more than one micronutrient or including improvement in public health measures. Second, the committee and workshop participants agreed to base all findings and recommendations in this report on the data provided in three background papers, because these documents provided the substantive basis for discussion at the workshop. "Conventional wisdom" was not considered a sound basis for judgment in the absence of acceptable evidence. To streamline discussion, no references are provided in this chapter; the interested reader is encouraged to read the supporting papers.

THE IMPORTANCE OF IRON, VITAMIN A, AND IODINE TO HEALTH

The health and vitality of human beings depend on a diet that includes adequate amounts of certain vitamins and minerals that promote effective functioning of physiologic processes, including reproduction, immune response, brain and other neural functions, and energy metabolism. The body needs relatively minute quantities of these elements—i.e., measured in micrograms or milligrams—thus supporting their description as micronutrients. These elements are essential; they cannot be manufactured by the human body and must be obtained through dietary means. Deficiencies of most micronutrients are known to have devastating effects on health. They increase risk of overall mortality and are associated with a variety of adverse health effects, including poor intellectual development and cognition,

decreased immunity, and impaired work capacity. The adverse effects of micronutrient malnutrition are most severe for children, pregnant women, and the fetus.

This report focuses on lessons learned from past interventions to address iron, vitamin A, and iodine malnutrition. The committee decided to limit its evaluation to these three micronutrients because it felt there was adequate experience for each and, because iron, vitamin A, and iodine deficiencies alone are responsible for significant global mortality and morbidity. While discussion relates to these three micronutrients, workshop participants agreed that the lessons learned for improving future intervention strategies would also be applicable to prevention and control of malnutrition created by deficiencies of other micronutrients.

Iron

Iron is present in both heme and nonheme forms in the diet. Heme iron, the most bioavailable form, is found in the greatest quantities in animal sources such as red meat. Normal individuals absorb between 20 and 30 percent of dietary heme iron, while iron-deficient subjects absorb between 40 and 50 percent. Nonheme iron—which is absorbed less efficiently than heme iron—is most abundant in other sources of iron, including eggs and all vegetable roots, seeds, leaves, and fruits. Nonheme iron is also present in heme iron-containing and other animal tissues. Nonheme iron generally constitutes over 90 percent of dietary iron, particularly in the developing world. In contrast with heme iron, nonheme iron absorption is enhanced or inhibited by many dietary constituents. Heme-iron-containing proteins, ascorbic, malic, tartaric, and succinic acids, and many fermentation products are enhancers. Meat and alcohol, by promoting gastric acid production, also enhance nonheme iron absorption. Inhibitors include fiber, phytic acid and other polyphosphates, calcium, manganese, polyphenols such as tannins and other compounds present in food (seeds, other plant components, and many condiments), and beverages (e.g., tea, herbal infusions, coffee, and chocolate).

ID has serious adverse consequences on health; the most evident is anemia. About one billion people worldwide suffer clinical anemia. Severe anemia causes as many as one in five maternal deaths and is a major cause of childhood mortality in many developing countries. Other consequences of iron deficiency are impaired physical growth; potentially permanent adverse effects on neurological functions involving cognition, emotional behavior, reaction to and reception of stimuli, attention span, learning capacity, and neuromotor development and function; decreased capacity for physical work; lowered immunity, resulting in increased susceptibility to infections; and alterations in the reproductive process.

Vitamin A

Vitamin A activity is found in fruits and vegetables that contain green and yellow provitamin A carotenoid pigments and as the preformed vitamin in liver and breast milk. Humans need less than 1 milligram of vitamin A a day to maintain health, yet in 1995, it was estimated that 3 million children annually exhibit xerophthalmia—that is, they are clinically vitamin A-deficient and at risk of blindness. An additional 250 million children under 5 years of age were estimated to be subclinically vitamin A-deficient (based on the prevalence of serum retinol distributions below 0.70 μmol/L) and at risk of severe morbidities and premature death. These estimates do not include pregnant and lactating women living in areas of childhood VAD endemicity who are also likely to be in poor status, but for whom epidemiological data are quite limited. A high prevalence of maternal night blindness and low breast milk levels of vitamin A are reported in such areas. A lack of sensitive, survey-applicable, nonclinical indicators specific to VAD, however, has hampered population-based evaluation of status among reproductive-age women and other age and sex groups.

Iodine

Iodine must be obtained from the environment, but it has been depleted from the soil and water in many areas of the world. WHO has estimated that over 1.5 billion persons in the world reside in regions of environmental iodine deficiency and are at risk of IDD. The only recognized role of iodine in mammalian biology is as a component of the thyroid hormones, although there are data suggesting that iodine deficiency may be involved in fibrocystic disease of the breast. IDD is associated with goiter, cretinism, mental and neuromotor retardation, and reproductive impairment. Fetal and pre- and postnatal survival are also reduced by iodine deficiency.

THE CONTINUUM OF POPULATION RISK

The nutrition status of all populations is in flux. Groups are in continuous movement along a continuum of nutritional risk, extending from a situation of severe micronutrient malnutrition, through a wide spectrum of presumed nutrient adequacy, to one of nutrient overload and toxicity. The latter state is not emphasized in this report. The committee has identified four levels of population risk.

- Level IV (severe deficiency) is characterized by populations with severe micronutrient malnutrition. These populations can be said to be in public health crisis with respect to vitamin A and iodine deficiency when clinical

manifestations (xerophthalmia and goiter) are prevalent at the levels indicated in Table 2-1. Immediate therapeutic and prophylactic programs are needed. There is lack of consensus on the prevalence cutoff to determine the urgency for therapeutic public health programs for anemia defined by hemoglobin level alone.[5]

- Level III (moderate deficiency) is characterized by populations with moderate to severe micronutrient malnutrition where preventive or therapeutic public health programs geared to the level of severity are appropriate. This scenario is most frequently encountered in developing countries, but it can be found in regions of industrial countries as well.
- Level II (mild and widespread deficiency) is characterized by populations with mild micronutrient malnutrition. This scenario is encountered in both developing and industrialized countries.
- Level I (mild and clustered deficiency) is characterized by only selected, usually deprived, populations affected by micronutrient malnutrition. This scenario is most frequently encountered in regions of industrial countries.

Table 2-1 provides the criteria for classification of populations to Levels IV to I for iron, vitamin A, and iodine status. In using this framework, program funders—and implementers—should note that populations within a single country may be at different levels of risk for these three micronutrients. For example, a given country may have populations at Level II with respect to iodine status, while the same or other populations are at Level III with respect to iron status. The criteria in Table 2-1 are based on prevalence rates of specific clinical and subclinical signs of iron, vitamin A, and iodine deficiency in specified subpopulations. In studies in the field, standard clinical signs for deficiency of iron, vitamin A, and iodine, respectively, are: anemia in any high-risk group; xerophthalmia in preschool-age children, including night blindness; and presence of goiter in school-age children as determined by palpation or ultrasound. The subclinical indicators for deficiency of iron, vitamin A, and iodine, respectively, are: iron deficiency indicator (usually serum ferritin); serum retinol level; and median urinary iodine concentration. The highest level of population risk assigned by a prevalence value takes precedence.

[5] Hemoglobin is a biochemical measurement that in some populations may not closely correlate with adverse health consequences at the cutoff used for defining anemia (e.g., when the hemoglobin distribution curve is narrow reflecting most values at the cutoff or only slightly below). When the distribution curve is skewed to the left, the risk of adverse health effects and need for public health interventions become increasingly urgent. Level IV, therefore, refers to a situation with a hemoglobin distribution substantially skewed toward the left.

TABLE 2-1 Population Prevalence of Clinical and Subclinical Signs of Iron, Vitamin A, or Iodine Deficiency by Level of Population Risk

Level of Population Risk	Indicator	Iron	Vitamin A	Iodine
IV (severe deficiency)	Clinical[a]	≥40% or	≥5% or	≥30% or
	Subclinical[b]	≥80–100%	≥20%	>99%
III (moderate to severe deficiency)	Clinical	≥20 to <40% or	≥1 to <5% or	≥20 to <30% or
	Subclinical	≥50 to <80%	≥10 to <20%	≥50 to <99%
II (mild and widespread deficiency)	Clinical	≥12 to <20% or	≥0 to <1% or	>5 to <20% or
	Subclinical	≥30 to <50%	≥2 to <10%	≥20 to <50%
I (mild and clustered deficiency)	Clinical	<5% and	0 and	≤5% and
	Subclinical	<12%	<2%	<20%

NOTE: Highest level assigned by a prevalence value takes precedence. For example, a population with 15% of its people showing clinical signs of iron deficiency (a Level III designation), but with 60% of its people showing subclinical signs of iron deficiency (a Level IV designation) would be classified as Level IV.

[a] Clinical: iron = prevalence of anemia in any high-risk group; vitamin A = prevalence of xerophthalmia in preschool-age children, including night blindness; iodine = prevalence of goiter in school-age children as determined by palpation or ultrasound.

[b] Subclinical: iron = prevalence of iron deficiency indicator below cutoff (usually serum ferritin); vitamin A = prevalence of serum 28retinol levels ≤ 0.7 µmol/L; iodine = prevalence of median urinary iodine values <100 µg/L.

SOURCES: WHO/UNICEF/UNU. 1997. Indicators for Assessing, and Strategies for Preventing, Iron Deficiency (WHO/NUT/96.12) Geneva: WHO. WHO. 1996. Indicators for Assessing Vitamin A Deficiency and Their Application in Monitoring and Evaluating Intervention Programs (WHO/NUT/96.10) Geneva: WHO. WHO/UNICEF/WHO/UNICEF/ICCIDD. 1994. Indicators for Assessing Iodine Deficiency Disorders and Their Control Through Salt Iodization (WHO/NUT/94.6) Geneva: WHO.

The rationale for classifying populations across the three micronutrients examined in this report is an important one. Although the interventions for the three will differ, it was the consensus of the workshop participants that micronutrient deficiencies tend to cluster in populations. Thus, intervention programs should always consider strategies that meet the population needs with respect to multiple deficiencies where they may exist. While interventions on a single micronutrient may, in certain instances, be appropriate (for example, USI), the committee believes that strategies that focus only on a single micronutrient, without consideration of other micronutrient needs, should no longer be supported without careful consideration and justification.

In addition, the focus on both clinical and subclinical signs as criteria for determining severity of micronutrient status is a deliberate one. Workshop participants concluded that the prevailing focus of past intervention efforts on frank clinical signs of micronutrient malnutrition as a basis for determining need, while important for their severe health consequences and for serving as indices of risk in the community, has often resulted in neglect of the vast hidden problem of subclinical micronutrient malnutrition. The subclinical problems contribute to slowed human capital development and stagnant national economic development through reduced mental and work capacities and premature deaths. Future efforts should therefore place particular emphasis on the measurement, control, and ultimate prevention of subclinical deficiencies.

The purpose of any intervention program is to move at-risk populations along the continuum of risk, from higher to lower levels of risk (toward Level I). As this chapter will demonstrate, experience has shown that the timeframe for movement will depend both on the context of overall national development of the target population's country and the mix of interventions selected within that context.

OPTIONS FOR SUCCESSFUL INTERVENTIONS

Past experience with strategies directed toward correction of iron, vitamin A, and iodine deficiencies demonstrates that there is a "toolchest" of potentially effective, complementary interventions available to both government and the private sector. Workshop participants agreed, however, that the key to past programmatic successes has not been just the availability of these tools—many programs have faltered even with their use. Experience suggests that it is the selection and adoption of the right *mix* of tools for a particular country or regional setting that can ensure success. Equally important, evaluation of limited past experience suggests that it is the persons and organizations using the tool that provide the critical means for building upon and extending the initial basis for success. Well-cited instances (see, for example, the description of the Thailand ivy gourd project in Chapter 4) support the contention that it is important that the people using the tools—ideally, providers at the local, regional, and

country level—have a say in their choice, are educated as to their strengths and limitations in different circumstances, and are assured the means and capabilities to maintain the tools long after their donors have moved elsewhere. This may be achieved by building local "ownership," as would be done for many food-based or supplementation interventions, or by utilizing a viable industrial base and market, as might be the case for fortification. Although logical and popular, workshop participants agreed that this contention requires additional confirmation, given its limited testing and the considerable additional costs associated with securing and maintaining broad-based community involvement.

Availability of the toolchest alone, however, has not been sufficient to ensure program success. Workshop participants agreed that careful consideration and application of design and management strategies suited to local conditions and needs are critical to success. Unfortunately, these strategies have not often been given adequate consideration in the design of past interventions.

The following section describes some of the major tools available in the fight against micronutrient malnutrition. It should be emphasized that each has its strengths and limitations and domain of applicability, providing a powerful mix of options for improving micronutrient status in a population over varying periods of time.

Supplementation

Supplementation refers to the addition of pharmaceutical preparations of nutrients—capsules, tablets, or syrups—to the diet. Research has shown supplementation of adequate dosage and duration to be efficacious in treating, correcting, and preventing deficiencies of iron, vitamin A, and iodine for groups in which there are serious health problems. A major challenge is to scale up supplementation to a program level that achieves adequacy in target group coverage, dosage, and frequency of dosing that assures effectiveness, representing the combined impact of efficacy and the process of implementation. Supplementation has traditionally been considered "short-term," although it may usefully continue until effective alternatives are in place. Iron supplementation and iron therapy are currently part of the national health programs in the majority of developing countries and in many industrial countries. Periodic distribution of high-dose vitamin A supplements, either universal to all children of a specified age range or targeted to high-risk groups, has been the most widely applied intervention for treatment, prevention, and control of VAD. Supplementation of iodine using iodized oils by injection; drops of Lugol's solution; and tablets of salts of iodine, sometimes disguised with chocolate, have been less frequently used than supplementation for iron and vitamin A, but it can be an effective stopgap measure in populations with severe iodine deficiency until salt iodization can become effective.

Strengths of supplementation include its immediate impact on micronutrient status, health, and survival ability. It can achieve rapid coverage in at-risk populations and be linked to the health care delivery system, and the cost of worker training is relatively low, compared, for example, with that for dietary modification. A key limitation of supplementation—whether it is used to correct for deficiencies of iron, vitamin A, or iodine—is that because of inadequate targeting or coverage, deficient individuals may not be identified or reached routinely, and many at-risk persons, particularly in rural settings, can be missed. In addition, periodic high coverage has often not been sustained over time for a variety of reasons, including lack of sustained financial or political support or other overriding priorities in a limited health infrastructure. Finally, poor compliance by the target individual in taking a supplement has been a consistent reason for the low impact of many supplemental schemes. This is a particular problem in iron programs, which have traditionally relied on the use of daily iron supplementation, although weekly dosing now appears to offer a cost-effective alternative. Thus, supplementation should be considered an essential and complementary bridge to more sustained measures such as food fortification, food-based approaches, and other supportive public health interventions. The example of Indonesia, which successfully shifted from an almost exclusive reliance on vitamin A supplementation to more varied strategies, such as fortification (see Chapter 4), supports this conclusion.

Fortification

Fortification refers to the addition of needed micronutrients to foods. Adequate consumption of fortified food has been shown to improve micronutrient status. The choice of a food vehicle or vehicles depends on a series of factors, including the target group, food consumption patterns of the target group, and availability and characteristics of the possible vehicle. With respect to the target group, food vehicles may differ when directed to the population as a whole (general fortification) or to specific target groups (e.g., infants, schoolchildren, and refugees), or defined socioeconomic or geographical areas (for example, urban, rural, and ethnic group). The fortified food should also be adjusted to match the food consumption practices of the target population to avoid under- or over-supplementation. Foods should be selected for fortification on the basis of the food consumption practices, stability, production and marketing characteristics, and cost.

Experience has shown food fortification to be a useful bridge to sustainable, long-term dietary change in populations at moderate and low levels of iron and vitamin A deficiencies (Level III to I). If the program is made universal through a commonly consumed product, fortification requires little government involvement in the creation of consumer demand or in the training of service delivery

workers. In addition, it generally presents fewer logistical problems in supply than supplementation and its costs end up being borne almost exclusively by the private rather than the public sector. The experience with iron fortification is mixed. When cereal flour is used without long storage time, ferrous sulphate is cheap and effective, and ethylene diamine tetraacetic acid (EDTA) iron could potentially be a satisfactory fortificant once supply and cost issues are solved. Nevertheless, iron fortification of foods continues to be plagued by the absence of ideal compounds that would be favorably absorbed, stable and nonreactive, with little color and taste of their own, easily measurable for monitoring purposes, and inexpensive. The experience with vitamin A fortification of foods has also been mixed. Successful vehicles for vitamin A fortification have included sugar in Guatemala and margarine in the Philippines. Experience with the use of vitamin A-fortified monosodium glutamate (MSG) in the Philippines and Indonesia—where the product was highly effective, but showed color changes (yellowing) that the manufacturers feared would jeopardize sales—suggests that it is important to solve technical problems with the vehicle early on, while assuring that the population with the micronutrient problem consumes the vehicle in stable quantities on a regular basis. Selection of the form of the fortificant is important. For iodine and vitamin A, the options are more straightforward than for iron. With iron, no one form is superior in all vehicles and environmental conditions. Thus, careful evaluation of options is required before the most appropriate iron fortificant is selected. The advantages outlined for salt in the following paragraph are also true for iron fortification of flour in some countries, and in vitamin A fortification of sugar. The same quality assurance precautions are required.

Fortification of salt with iodine has been a major public health success. It has the unique advantage among the micronutrients because it requires no change in dietary habits in most instances: everyone uses salt. USI has therefore become the cornerstone for prevention of IDD. Programs, however, must take into account possible losses between point of manufacture or importation and the consumer's table. Losses may vary among the forms of iodine used (iodide vs. iodate), heat, purity, humidity, packaging, shelf time, and losses in cooking. Programs should also be designed around salt consumption patterns in order to ensure, as nearly as possible, an intake of iodine within the desired range. Similarly, a major need in the salt iodization process is keeping the level of added iodine within safe and effective limits. This means that, at the very least, the concentration of the commercial product must be measured at frequent intervals. Fortunately, the measurement technique is quite simple and reasonably accurate for practical purposes. Difficulties arise in implementing programs when the salt industry is widely dispersed among a large number of small producers. Ensuring distribution of iodine to all local producers is difficult, and compliance is a problem. Other foods that have been used successfully as vehicles for iodine

fortification have included bread and water. Salt, however, remains the preferred vehicle for fortification.

A less traditional form of intervention is the broad class of plant breeding strategies that are emerging to deal with micronutrient deficiencies. A number of pilot trials are now under way worldwide to examine nutrient-modified crops —high-iron rice is an example—to address serious micronutrient deficiencies. In addition, reduced phytate staple crops are being developed to increase the bioavailability of a range of micronutrients. If successful, these strategies are attractive because they do not require a modification in typical dietary patterns.

Food-Based Approaches

Food-based approaches attempt to correct the underlying causes of micronutrient deficiencies. These strategies are usually considered the ideal long-term goal toward which society strives—provision or assurance of access to a nutritionally adequate diet achieved through diversity of food availability, wise consumer selection, proper preparation, and adequate feeding. Nevertheless, the conventional assumption that food-based approaches represent the best strategy for correcting micronutrient deficiency in all circumstances needs to be reviewed carefully. If increases in homegrown foods can be effected, and this leads to increased intakes, then the dietary change minimizes the effect of lack of consumer access to markets or fluctuations in market prices or food availability. Increased reliance on food-based approaches decreases reliance on the health care system as a means of nutrient supply (as with supplementation) and offers a source of nutrients through foodstuffs that may be available through foraging as well as homegrown or procured foods. In the case of iodine deficiency resulting from the low iodine content of water supplies and locally produced foods, however, dietary change based on local foods is not an option. Changes in food-based strategies also have only limited, short-term application for the prevention of iron deficiency when there are economic or religious constraints on increasing animal protein intake. In addition, efforts to change national consumption patterns of foods that interfere with iron uptake (e.g., tannin containing teas, wheat-containing foods) have had limited success. Addition of iron enhancers to the diet (vitamin C) is also being tried, but experience is limited. Studies have also shown that improving iron status as part of the complementary feeding of infants and very young preschoolers is impractical without fortification. For improving vitamin A status, food-based approaches could be most effective where there is widespread availability, variability, adequacy, and acceptability of vitamin A-containing foods among targeted populations.

The cultivation of homegrown foods is not cost-free. In most cases the responsibility for cultivation rests with the females in the household. The issue of

time constraints on women must be a key consideration in assessing the feasibility of home gardens to alleviate micronutrient deficiencies.

To at least some extent, past experience has shown that dietary modification can be brought about by nutrition education. To even begin to achieve such changes, however, may require five to ten years or more, assuming a stable economic and political environment. Dietary modification and changes depend not only on changes or modifications in agricultural activities such as crops raised and food production, but also on food marketing, preservation, and preparation. A critical institution is the infrastructure of the communications industry, including those who produce mass media and point-of-purchase advertising that may influence dietary change. Advertising and other advocacy measures should, however, be based on principles of sound nutrition.

Other Public Health Control Measures

Disease control methods—including immunization, parasite control, provision of sufficient water and public sanitation, control of diarrheal diseases and acute respiratory infections (ARI), and the teaching of personal hygiene and sanitation practices—are an important addition to, but should not be considered a replacement for, interventions that increase the micronutrient intake of deficient populations. For example, high measles immunization coverage can contribute importantly to VAD control, as documented in Tanzanian children by the threefold reduction in hospital admission for corneal ulceration associated with improved coverage (see Chapter 4). Similarly, treatment of hookworm infection and prevention of reinfection have been shown to decrease iron loss, and thus complement iron replenishment strategies (see Chapter 3). Since correction of micronutrient deficiency, in turn, improves response to immunization and other public health measures, simultaneous attention to improving nutrition status and ensuring effective public health measures can offer the most cost-effective interventions in deprived populations.

COSTS OF INTERVENTIONS

One of the most severe limitations in evaluating past strategies for prevention or correction of micronutrient malnutrition is the widespread lack of information on cost-effectiveness. The data that do exist suggest that interventions against micronutrient malnutrition, considered either separately or in any combination, offer a high return for a relatively low investment.

The following two tables derive from the 1994 World Bank report, *Enriching Lives*.[6] Table 2-2 indicates that the direct costs of delivering nutrients as supplements or as fortified foods are low. In India and Guatemala, it cost US $0.12/year per person (in 1994 U.S. dollars) to fortify salt and sugar, respectively, with iron. In Guatemala, the costs of fortifying sugar with vitamin A were US$0.17/year per person. In India, it cost US$0.05/year per person to fortify salt with iodine.

The costs of dietary change are less well documented than those of fortification and supplementation; most data derive from studies of vitamin A interventions (see Chapter 4). A project conducted in Nepal attempted a cost-effective analysis of three vitamin A interventions: semiannual capsule distribution, capsule distribution piggy-backed to primary health care (PHC), and nutrition education activities piggy-backed to PHC. Distribution of vitamin A supplements was least costly, followed by PHC and nutrition education. Similarly, when costs and effectiveness of three vitamin A interventions—sugar fortification, capsule distribution, and gardening plus nutrition education—were examined in a study in Guatemala, the analysis reported cost per high-risk person achieving adequate vitamin A status to be US$0.98/year for fortification, US$1.86/year for capsule distribution, and US$2.71/year to US$4.16/year for gardens. For the pilot HI Bangladesh gardening project, annual cost/target family averaged US$39.0/year. When disaggregated to an individual garden level that included operating costs for seeds/seedlings, crop protection (fencing), and irrigation, US$11.7/year was spent; minus fencing and irrigation, the cost was US$3.0/year. The scaled-up national project, working through Bangladeshi nongovernmental organizations (NGOs), has reduced costs to an estimated US$8.33/garden, or US$1.5/individual.

Costs in life years gained from reductions in mortality and/or lived free of illness and disability (disability-adjusted life years, or DALY[7]) provide a similar

[6] World Bank. 1994. *Development in Practice: Enriching Lives: Overcoming Vitamin and Mineral Malnutrition in Developing Countries*. Washington, D.C.: The World Bank.

[7] The DALY is an indicator of the time lived with a disability and the time lost through premature mortality. Years lost due to premature mortality are estimated in the context of the standard expectation of life at each age. Years lived with disability are translated into an equivalent time loss through multiplication by a set of weights that reflect reduction in functional capacity. In both cases, the losses are weighted according to a particular set of "value choices"—the value of time lived at different ages (age weights) and time periods (discounting). (For a fuller justification of the conceptual framework underlying the DALY, see Murray, 1994, and Murray and Lopez, 1996.)

Murray, C. J. L. 1994. Quantifying the Burden of Disease: The Technical Basis for Disability-Adjusted Life Years. *Bulletin of the World Health Organization* 72(3):429–445.

Murray, C. J. L., and Lopez, A.D. 1996. *Global Burden of Disease and Injury, Vol. 1*. Boston: Harvard University Press.

picture (see Table 2-3). Fortification with iron costs US$4 per DALY saved; with iodine, US$8 per DALY saved; and with vitamin A, US$29 per DALY saved. The costs of supplementation are also relatively low. Providing pregnant women with supplemental iron costs US$13 per DALY earned, while supplementing all people under age 60 with iodine costs US$37 per DALY earned. Vitamin A supplementation of children under age 5 costs US$9 per DALY earned.

TABLE 2-2 Costs of Micronutrient Control Programs

Micronutrient	Country/Year	Estimated Cost in US$/Person (1994$)	Estimated Cost per Person per Year of Protection (1994 $)
Iodine			
Oil injection	Peru 1978	2.75	0.55
Oil injection	Zaire 1977	0.80	0.17
Oil injection	Indonesia 1986	1.25	0.25
Water fortification	Italy 1986	0.05	0.05
Salt fortification	India 1987	0.02–0.25	0.02–0.05
Vitamin A			
Sugar fortification	Guatemala 1976	0.17	0.17
Capsule	Haiti 1978	0.27–0.41	0.55–0.81
Capsule	Indonesia/ Philippines 1975	0.25	0.50
Gardening, plus nutrition education	Guatemala 1994 (high-risk persons)	2.71–4.16	n.a.
Iron			
Salt fortification	India 1980	0.12	0.12
Flour fortification	Turkmenistan 1977	0.16	n.a.
Sugar fortification	Guatemala 1980	0.12	0.12
Sugar fortification	1980	1.00	1.00
Tablets	1980	3.17–5.30	3.17–5.30

SOURCES: World Bank. 1994. *Development in Practice: Enriching Lives: Overcoming Vitamin and Mineral Malnutrition in Developing Countries*. Washington, D.C.: The World Bank.; except for (Guatemala 1994) Phillips, M., T. Sanghvi, R. Suárez, J. McKigney, V. Vargas, and C. Wickham. 1994. The Costs and Effectiveness of Three Vitamin A Interventions in Guatemala, Final Report. Working Paper No. 2 Nutrition Cost-Effectiveness Studies, USAID, Washington, D.C.; (flour fortification) Gary Gleason, 1997, UNICEF Central Asian Regional Office, Almaty, Kazakstan, personal communication.

In summary, all the cost-effective evaluations reviewed agree that fortified foods or capsule distribution, depending on whether a fortifiable food, widely consumed by the high-risk group, is available, are potentially the least expensive interventions. Although fortified foods are likely to be the more sustainable investment, they require a food production or delivery infrastructure that may be lacking in many countries. Capsule distribution is a proven, time-limited (except in the case of iron supplementation in pregnancy), and cost-effective intervention if coupled with programs that have effective service delivery to target groups and there is a consistent, adequate supply. Promotion of increased consumption and/or production of food is a viable option in most contexts where water supply is not critically short, but it requires application of a social marketing methodology to overcome socioeconomic-cultural barriers to behavior changes where benefits are not always obvious. There are many difficulties in quantifying nonmonetary benefits in order to realistically estimate the cost–benefit ratios associated with each intervention. Nonetheless, over the long term, interventions that provide balanced, multinutrient improvements, such as nutrient-rich, natural and/or fortified foods, are most likely to provide permanent benefit to recipients dwelling in deprived contexts.

TABLE 2-3 Returns on Nutrition Investments

Deficiency/Remedy	Cost per Life Saved ($)	Cost per Disability-Adjusted Life Year Gained
Iron deficiency		
Supplementation of pregnant women only	800	13
Fortification	2,000	4
Iodine deficiency		
Supplementation (reproductive-age women only)	1,250	19
Supplementation (all people under age 60)	4,650	37
Fortification	1,000	8
Vitamin A deficiency		
Supplementation (under age 5 only)	325	9
Fortification	1,000	29
Nutrition education	238	n.a.
Nutrition education and maternal literacy	252	n.a.

SOURCE: World Bank. 1994. *Development in Practice: Enriching Lives: Overcoming Vitamin and Mineral Malnutrition in Developing Countries* . Washington, D.C.: The World Bank.

FEASIBILITY OF INVOLVING KEY SOCIETAL SECTORS IN THE PLANNING AND IMPLEMENTATION OF MICRONUTRIENT INTERVENTIONS: A GUIDE TO DECISIONMAKING

Experience has shown that different strategies for prevention and control of micronutrient malnutrition are required for countries at different levels of development. Key elements for successful implementation of food fortification programs and for achieving sustainable longer-term dietary change include (1) the presence of a viable food industry; (2) available channels for food marketing and distribution; (3) a health care system that can help identify and monitor micronutrient malnutrition in the population and provide education and treatment for deficiencies; (4) an effective core community of persons that can provide necessary input into the planning, implementation, and evaluation of intervention programs and enhance the kinds of educational, marketing, and community outreach activities that will help ensure sustainability of the intervention over the longer term; and (5) for long-term dietary change, a level of population literacy that can allow for greater community involvement in decisionmaking and conduct of intervention programs (see Chapter 4 on vitamin A).

Table 2-4 presents the degree of availability and accessibility of these five elements across four levels of country development and for urban and rural populations as separate groups. The four levels of country development are: very poor countries, poor countries, middle-income countries, and industrial countries. This table can be used by local experts, in consultation with international donors, to help identify optimal approaches to intervention.

Table 2-4 indicates that, for very poor countries, availability and access to established food industries, food marketing or distribution channels, health care systems, and developed community organizations are restricted. The overall level of literacy is also relatively low. Expertise that may be brought to bear on the planning and implementation of interventions tends to be more concentrated among relatively few individuals.

The experience for poor countries is slightly better overall; access and availability are increased for all elements. Access to the health care system is increased in urban settings and the presence of effective community organizations is greater, as is the level of literacy. While there are some notable exceptions, where access to health care increased in low-income countries (e.g., Cuba and Sri Lanka), these examples are rare. Generally, as national income increases, availability and access to basic health services increase.[8]

It is in the middle-income countries that the presence of established food industries (in urban settings) and food marketing and distribution channels becomes more pronounced. Health care is more widely accessible in both urban

[8] World Bank. 1993. *World Development Report 1993: Investing in Health*. New York: Oxford University Press for the World Bank.

and rural settings and there tends to be organized community activity. Rates of overall literacy are increased.

The five elements are well developed and established in industrial countries.

ELEMENTS OF SUCCESSFUL INTERVENTIONS ACROSS THE CONTINUUM OF POPULATION RISK

This section and its accompanying tables combine information from the last three sections and offer a guide to the preferred initial approaches to prevention and control of iron, vitamin A, and iodine deficiencies in populations at the defined levels of risk. Workshop participants agreed on two guiding principles in developing these approaches. First, planning for sustained intervention should include consideration of all four strategies—supplementation, fortification, food-based approaches, and public health control measures—where appropriate and feasible. Only the relative emphases among the four approaches should differ, both by level of population risk and by phase of intervention. Second, the long-term goal of intervention should be to shift emphasis away from supplementation and toward a combination of food fortification (USI or iron-fortified flour, for example) and food-based approaches where appropriate and feasible to sustain change. In other words, as populations move along continuums of risk and resource availability, the relative mix of interventions should model those presented in the following four tables for the level indicated. Inherent in this categorization, however, is the implicit caveat that the most appropriate intervention is influenced by the targeted age group. An obvious example is that of a 6-month-old, severely anemic child who will likely be unaffected by a wheat iron-fortification program.

Interventions for Level IV Populations

For country planners and donors developing interventions for Level IV populations, Table 2-5a suggests that supplementation be given primacy as a first step. Supplementation should be universal in the case of iron and vitamin A. The potential for toxicity of iodine supplementation in individuals with normal iodine levels argues for an approach that is more closely targeted to vulnerable groups.

The mix of preferred approaches in Level IV populations should also stress USI where feasible, as well as opportunities for household-processed, food-to-food fortification of complementary and weaning foods that take advantage of traditional home and community preservation practices.

Intervention programs should also include elements directed toward changing the diets of the target populations. More attention should be paid at this stage to enhancing family capacity to grow nutrient-rich foods.

TABLE 2-4 Feasibility of Involving Key Societal Sectors in the Planning and Implementation of Micronutrient Interventions: A Guide to Decisionmaking

	Food Industry		Food Marketing or Distribution Channels		Health Care System		Community Organization		Literacy Level
Context	Rural	Urban	Rural	Urban	Rural	Urban	Rural	Urban	(% of pop.)
Very poor countries	Nil	Very limited	Restricted	Limited	Minimal access	Limited access	Limited structure and participation		< 25
Poor countries	Minor	Limited	Limited regionally	Limited	Limited access	Moderate access	Some participation		<50
Middle-income countries	Limited availability	Developed	Good regionally	Good nationally	Accessible		Organized, with community participation		<75
Industrialized countries	Developed		Well-developed		Highly accessible		Highly organized		>95

TABLE 2-5a Preferred Initial Approaches to Prevention and Control of Iron, Vitamin A, and Iodine Deficiencies in Populations with Severe Micronutrient Malnutrition—LEVEL IV

Approach	Deficiency		
	Iron	Vitamin A	Iodine
Supplementation			
Targeted to vulnerable groups	—	++	++++
Universal	++++	++++	—
Fortification			
Targeted foods	+	+++	—
Universal	—	—	+++
Food-based approaches			
Food, nutrition education	+	++	+
Food production	++	+++	n.a.
Food-to-food	++++	++++	—
Public health control measures			
Immunization	++++	++++	—
Parasite control	+++	++	—
HW/S	+++	—	—
DD/ARI	+++	+++	—
Personal sanitation/hygiene	++++	++++	—

NOTE: ++++, very strong emphasis; +++, strong emphasis; ++, moderate emphasis; +, light emphasis; —, no emphasis; food-to-food fortification, mixing of staple foodstuffs—e.g., mango with gruel—at the household level to enrich nutrient content; n.a., not applicable; HW/S, healthy water and public sanitation; DD/ARI, control of diarrheal diseases and acute respiratory infections.

Public health measures that aim to control infectious diseases—for example, treatment of hookworm infection and prevention of reinfection and increasing measles immunization coverage—should be considered an essential complement to interventions for iron and vitamin A, respectively.

Interventions for Level III Populations

Preferred approaches to combating micronutrient malnutrition in Level III populations include movement away from complete reliance on universal supplementation to a greater emphasis on supplementation of vulnerable groups.

TABLE 2-5b Preferred Initial Approaches to Prevention and Control of Iron, Vitamin A, and Iodine Deficiencies in Populations with Moderate to Severe Micronutrient Malnutrition—LEVEL III

Approach	Deficiency		
	Iron	Vitamin A	Iodine
Supplementation			
Targeted to vulnerable groups	+++	+++	++
Universal	++	+	—
Fortification			
Targeted	—	—	—
Universal	+	++	++++
Food-based approaches			
Food, nutrition education	++	+++	+
Food production	+	++	n.a.
Food-to-food	+++	+++	—
Public health control measures			
Immunization	++++	++++	—
Parasite control	+++	++	—
HW/S	+++	++	—
DD/ARI	+++	++	—
Personal sanitation/hygiene	++++	++++	—

NOTE: ++++, very strong emphasis; +++, strong emphasis; ++, moderate emphasis; +, light emphasis; —, no emphasis; food-to-food fortification, mixing of staple foodstuffs—e.g., mango with gruel—at the household level to enrich nutrient content; n.a., not applicable; HW/S, healthy water and public sanitation; DD/ARI, control of diarrheal diseases and acute respiratory infections.

Programs should shift to a greater emphasis on food fortification relative to supplementation, particularly with regard to USI and, to a lesser degree, vitamin A and iron. National capacity to fortify and distribute foods should be exploited whenever possible, with continued attention directed to opportunities for household-processed, food-to-food fortification.

Food and nutrition education should become a more important part of the mix, while programs to enhance family capacity to grow nutrient-rich foods should continue to be stressed.

Public health control measures should continue to be considered an essential complement to interventions for iron and vitamin A.

Interventions for Level II Populations

In Level II populations, the relative mix of approaches begins to emphasize interventions that promote dietary change and programs that make use of expanding

national capabilities in food production and distribution. Supplementation programs directed toward vulnerable groups should continue for iron and vitamin A. USI remains the program of choice for iodine deficiency; fortification with vitamin A and iron can also be helpful, assuming some level of food processing—refining sugar, milling flour, and the like—in the target country.

Complementary public health measures to control parasitic and diarrheal diseases and ARI are generally not needed because of the usual absence of these diseases in Level II populations. Nevertheless, efforts directed toward maintaining immunization rates and ensuring sanitation and hygiene in home practices should continue to be stressed.

TABLE 2-5c Preferred Initial Approaches to Prevention and Control of Iron, Vitamin A, and Iodine Deficiencies in Populations with Mild and Widespread Micronutrient Malnutrition—LEVEL II

Approach	Deficiency		
	Iron	Vitamin A	Iodine
Supplementation			
Targeted to vulnerable groups	+++	++	+
Universal	—	—	—
Fortification			
Targeted	—	—	—
Universal	+++	++	++++
Food-based approaches			
Food, nutrition education	+++	++++	+
Food production	—	+	n.a.
Food-to-food	—	—	—
Public health control measures			
Immunization	++++	++++	—
Parasite Control	—	—	—
HW/S	—	—	—
DD/ARI	—	—	—
Personal sanitation/hygiene	++++	++++	—

NOTE: ++++, very strong emphasis; +++, strong emphasis; ++, moderate emphasis; +, light emphasis; —, no emphasis; food-to-food fortification, mixing of staple foodstuffs—e.g., mango with gruel—at the household level to enrich nutrient content; n.a., not applicable; HW/S, healthy water and public sanitation; DD/ARI, control of diarrheal diseases and acute respiratory infections.

TABLE 2-5d Preferred Initial Approaches to Prevention and Control of Iron, Vitamin A, and Iodine Deficiencies in Mild and Clustered Populations—LEVEL I

Approach	Deficiency		
	Iron	Vitamin A	Iodine
Supplementation			
Targeted to vulnerable groups	++	+	+
Universal	—	—	—
Fortification			
Targeted	—	—	—
Universal	+++	++	++++
Food-based approaches			
Food, nutrition education	++++	++++	++
Food production	—	—	n.a.
Food-to-food	—	—	—
Public health control measures			
Immunization	++++	++++	—
Parasite control	n.a.	n.a.	—
HW/S	n.a.	n.a.	—
DD/ARI	n.a.	n.a.	—
Personal sanitation/hygiene	++++	++++	—

NOTE: ++++, very strong emphasis; +++, strong emphasis; ++, moderate emphasis; +, light emphasis; —, no emphasis; food-to-food fortification, mixing of staple foodstuffs—e.g., mango with gruel—at the household level to enrich nutrient content; n.a., not applicable; HW/S, healthy water and public sanitation; DD/ARI, control of diarrheal diseases and acute respiratory infections.

INTERVENTIONS FOR LEVEL I POPULATIONS

Food-based approaches and food fortification are the approaches of choice to address micronutrient malnutrition in selected, usually deprived, populations of Level I countries. Programs directed toward iron and, to a lesser degree, vitamin A supplementation of at-risk groups should be continued as needed, as should universal public health control measures such as immunization and education on personal hygiene and sanitation.

Balancing Approaches to Country-Specific Circumstances

Countries with micronutrient deficiencies at a public health level are usually confronted with multiple problems of underdevelopment and limited resources to deal with them. Setting priorities is essential, not a choice. A series of notable

political events, beginning in 1990 with The World Summit for Children and the follow-up 1991 conference on Ending Hidden Hunger, focused world attention on micronutrient malnutrition. The preparatory process for the International Conference on Nutrition in 1992 and country-level follow-up actions have fostered national-level planning for micronutrient deficiency control that was virtually nonexistent in many countries before these high-profile political events. National planning often is done collaboratively with international and bilateral agencies because of reliance on their financial assistance for program follow-up. The caution is to ensure that internationally set, time-bound goals are driven by nationally determined, not donor-driven, considerations.

Coordinating Interventions Across Micronutrients

Malnutrition from a single micronutrient seldom occurs in isolation, but within the context of deprivation, including multiple vitamin/mineral deficits. Thus, it is attractive to conceive of dealing with all of these deficits concurrently. A careful analysis needs to be undertaken, however, to determine where program compatibility exists in areas of awareness, assessment, analysis of causes, and resources available for solutions. Coordinated strategies are technically feasible, but infrequently implemented.

Except for iodine, food-based approaches are the most logical for integrating micronutrient control programs. Interactions are avoided between potential concentrated-dose incompatibilities among supplements, such as solubility differences, susceptibility to oxidation, and competition for absorption. The situation with IDD control is different because the deficit is not correctable simply by growing more or a different variety of food in the same iodine-depleted area. Furthermore, there is a proven, cost-effective IDD control intervention—universal iodization of salt—that should receive continued support, using oral iodine supplements to control the problem in limited, unyielding situations. Nonetheless, there are areas of opportunity for cost-saving, complementary activities in assessment, program selection and design, and in delivery mechanisms to vulnerable groups where micronutrient deficiencies coexist.

COMMON ELEMENTS OF SUCCESSFUL MICRONUTRIENT INTERVENTIONS

This section briefly details elements that the workshop participants identified as being common to all successful micronutrient interventions (see Table 2-6).

Political Will/Stability

Experience demonstrates that political will and stability are important factors in the control of micronutrient deficiencies. Political instability breeds failure, as demonstrated

by the collapse of the initially successful Guatemalan salt fortification (iodine) and sugar fortification (vitamin A) programs following a period of political unrest. Working to ensure consistent signals from a broad spectrum of leadership affirming the importance of eliminating or reducing micronutrient disorders, however, can help catalyze both government and voluntary agency efforts. Key actors in this process are political and administrative leaders, those from the health sector, the business community, NGOs, and, when involved in such programs, international agencies. Respected and visionary local champions of the intervention should be sought and involved from the earliest stages of program development. These champions can be individuals, as was the case in the Ecuador salt fortification program, or industries, as was seen in the Nigerian salt fortification program. Political will can be further enhanced and maintained through the development of creative partnerships, such as that between the government of the Philippines and the private sector in the program to fortify margarine with vitamin A.

Strategic and Program Planning

A common element in the design and implementation of successful micronutrient programs is development of effective strategies and planning processes. Strategic planning results in a clear set of impact objectives to be reached over a set timeframe and the choice of interventions and the necessary scale of operations to achieve them within available resources. Program planning involves formulation of process objectives and work plans. Decisions include choices of scale, targeting to particular beneficiaries, phasing and sequencing of activities, and selection of technologies. The planning process also addresses development of effective systems for training, supervision, management and logistics, the framing of work routines, allocation of tasks and functions, and phasing and sequencing of activities. The successful experience in increasing use of the underutilized vitamin A-rich ivy gourd in Thailand was a good example. A majority of these elements were incorporated (see page 117). The flexibility to adapt program content to changing circumstances, including lessons of implementation experience, is also a characteristic of successful intervention programs.

Community Involvement, Participation, and Consumer Demand

Involvement of the community at the point where interventions and beneficiaries intersect is a feature of some successful micronutrient programs. An excellent example was the program promoting horticultural interventions in gardens in Bangladesh. Committees at the state, district, block, and village levels provided guidance, coordination, and implementation (see page 123). It also characterizes most of the programs that have had positive results against other forms of malnutrition. Opinion is divided as to when and how best to involve individual communities:

before the basic program framework is prepared or after. Both strategies appear to have helped to generate appropriate levels of consumer demand for interventions. Involving each community in the original design of its own interventions through such techniques as Participatory Rural Appraisal may fully invest program ownership in the community. The price, however, might be a diversity, which the program management system cannot easily absorb. Presenting a community with a design that has proved workable in similar circumstances may limit its involvement to adaptation, but has not proved a major impediment to beneficiary participation in the program.

Physical and Administrative Infrastructure

Experience shows that when interventions have been "scaled up"—that is, increased in size and/or duration—results may be disappointing, in part because of the failure to anticipate the management and institutional capacity needed for ongoing operation. To ensure larger-scale or sustained accomplishment, the physical and administrative infrastructure must be appropriate. Among the indications that these conditions exist are the following, which apply regardless of the intervention being considered:

- *Physical infrastructure*. This includes adequate communications capability (e.g. postal mail, telephones, faxes, e-mail; presence of roads, or other ways to reach the populations at risk) and special storage conditions where required.
- *Strategy and program design capability*. These include the ability to identify optional strategies and program designs, to test them out, to choose best alternatives, and to evaluate and adjust programs on the basis of appropriate operations and management research. Selection of the most appropriate strategies and program designs also requires the capacity to adapt them to specific resource environments and constraints, along with the ability to measure program costs, efficiency, and effectiveness, as well as costs foregone through intervention outcomes. Part of the strategy and program design process requires clear specification of roles for concerned organizations and institutions, as well as administrative accountability at all levels of managerial and implementation responsibility.
- *Scaling-up skills*. The initial success of many interventions is based primarily on the results of small-scale clinical trials. The ability to move to the national level from such small-scale endeavors needs to be validated through large-scale field demonstrations that include measures of effects.

TABLE 2-6 Common Elements of Successful Micronutrient Interventions

Element	Description
Political will/stability	Consistent signals from a broad spectrum of leadership; key actors in this process are political and administrative leaders, those from the business community, nongovernment organizations, and, when involved in such programs, international agencies.
Strategic and program planning	Strategic planning results in a clear set of impact objectives to be reached over a specific time frame and the choice of interventions and the necessary scale of operations to achieve them within available resources; program planning involves formulation of process objectives and work plans.
Community involvement, participation, and consumer demand	Experience has demonstrated that involvement of the community in all program phases, from initial design to evaluation, helps to generate appropriate levels of consumer demand for interventions.
Physical and administrative infrastructure	Presence of a competent physical infrastructure, strategy and program design capability, scaling-up skills (i.e., ability to move to national levels from smaller-scale, local endeavors), managerial capability, budgetary resources, and human resources.
Communications strategies	Ability to generate consumer demand for improved micronutrient status, to remove barriers to adoption of specific micronutrient-enhancing practices. Such strategies are critical to long-term program sustainability and effectiveness.
Use of appropriate food vehicle	Choice should take into account bioavailability, safety, side effects, and public acceptance; the technology should be consistent with best practice as determined by comparison with similar programs or well-documented research in pilot or clinical programs.
Sustainability	Three key factors include efficacy, appropriateness, and demonstrated feasibility.
Information systems, monitoring, and evaluation	Process and outcome indicators, including biological indicators, appropriate to monitor intervention impact will vary in accordance with the intervention objective.

- *Managerial capability*. Training to strengthen or develop a management ethic and skills, and to promote management institutional development, including systems for administrative control, is an important but sometimes overlooked factor that influences program success. The establishment of appropriate process goals and a system and procedures for periodically assessing progress toward them is an important measure of managerial capability.
- *Budgetary resources*. Resources consistent with achieving established impact objectives need to be made available. These include budgets adequate to develop, test, and choose among strategy options; to formulate and refine the program design; and to test and implement interventions at agreed operational levels for the time specified to reach program objectives.
- *Human resources.* The capacity to define tasks and workloads realistically, and to train, deploy, supervise, and retain both employees and, where appropriate, volunteers must also be considered. Task-oriented training needs to take place initially and on an in-service basis, particularly for workers and supervisors in service delivery programs that involve supplementation and communications. Food-based approaches involving dietary modification require appropriate training of formal and informal educators in the use of both interpersonal and mass media resources. Supervisory tasks and ratios need to be geared to service delivery tasks and work routines.

Communications Strategies

Communications can play an important role in successful micronutrient programs by inducing target groups to improve their micronutrient-related behaviors. Depending on the specific operational context, successful communications strategies seek to (1) generate consumer demand for improved micronutrient status and/or (2) remove barriers to adoption of specific micronutrient-enhancing practices. Such strategies are critical to long-term program sustainability and effectiveness.

Communications is an important supportive measure in supplementation and fortification. It can be both a supportive and a leading intervention in the area of dietary modification. In micronutrient supplementation regimes, motivating consumers to demand improved micronutrient status as a personal benefit can lead to higher coverage rates, better compliance, and more efficient implementation. Regarding fortification, public demand for better micronutrient status plays a part in both consumption of the fortified product and in encouraging administrative bodies to adopt and enforce quality-control and other regulatory mechanisms. In the area of dietary practices, appropriate communications interventions can persuade consumers to prepare existing menus in micronutrient-favorable ways and/or to diversify their diets to include new sources of micronutrients.

Successful communications strategies include: (1) market segmentation, that is, identification of groups whose attitudes and behavior are to be affected; (2) definition of the specific changes sought for each group; (3) understanding of the barriers to such changes; (4) selection of suitable communications channels; and (5) the development and testing of appropriate messages.

In most cases, a comprehensive communications strategy will need to address specific segments of the general public, with attention to both target groups for a given intervention and those who influence the micronutrient behavior of such groups. Health workers and managers, from the community to the tertiary care levels, would often need to be included in the strategy, and in most cases would require reorientation, training, and materials support to do so. The potential role of policymakers, particularly in health, agriculture, education, industry, and finance also would need to be analyzed, particularly when such officials could affect resource flows, public perceptions, or other key aspects of the communications process. Two good examples of successful use of communications strategies in building support for and implementing effective interventions were the joint iodine fortification/supplementation program in Ecuador (see page 180) and the experience in applying social marketing methods to increase use of locally available vitamin A-rich foods in Thailand (see page 117).

Use of Appropriate Vehicle

The choice of an appropriate vehicle for the micronutrient and/or intervention strategy selected should take into account bioavailability, safety, side effects, and public acceptance. The vehicle should be consistent with best practice as determined by comparison with similar programs or well-documented research in pilot or clinical programs.

An example of inappropriate choice of vehicle was the Indonesian experience of fortifying MSG with vitamin A (see page 133). Although the vehicle was universally applicable, the resulting fortified "yellow rather than white" product was unacceptable. The widely accepted use of iodinated oils in Ecuador (see page 180) and vitamin-A fortified margarine in the Philippines (see page 134) indicates, however, that selection of an appropriate food vehicle is an important determinant of program success. Genetically modified crops appear to offer opportunities to increase yield, increasing micronutrient content or bioavailability. Their acceptance by the public, however, needs to be addressed.

Sustainability

Sustainability, as used here, refers to both the continuity of a successful intervention and a continuation of a significant, positive impact on the intended beneficiary.

The first kind of sustainability thus relates to process, the other to outcomes.

Three factors are essential for sustainability: efficacy, appropriateness, and demonstrated feasibility. Clearly one would only want to sustain an intervention that has "worked." The assumption is that a policy or program has been implemented that addresses the micronutrient need of a particular population. In order to continue to effectively operate the intervention, an institutional structure is needed that will allow for ongoing capacity for management. One common finding in public health interventions, in general, is that successful approaches are the ones designed and managed as part of research and/or pilot projects.

Cost is clearly a factor that influences sustainability. Programs based on a permanent reliance on external funding are usually not viable in the long term. At the same time, precipitous withdrawal of external funding may also doom projects. A consistently agreed upon gradualist approach may be optimal. There are now examples of the effective transition from total donor funding to total support by financing at the national level. The Indonesia vitamin A program is an excellent example of an intervention that evolved over a 20-year period from 100 percent donor support to the current program, which is entirely funded by government monies. The time period is also critical. For most countries, it is unrealistic to expect this transition to occur in a 3- to 5-year period. Micronutrient interventions such as the Indonesia vitamin A program, in which the donors and the host country plan for this transition from the initial stages, are the ones that have been most successful.

Micronutrient interventions that continue to achieve a significant impact on the target individuals are projects that are flexible enough to respond to the changing needs of the client. Typically this involves a combination of approaches to address a particular micronutrient. For vitamin A, as an example, a combination of strategies is most effective in reducing vitamin A deficiency in a given area. Each country must determine the most cost-effective mix of interventions.

Information Systems, Monitoring, and Evaluation

Monitoring and evaluation are essential program elements. They are vital for ensuring and improving efficiency of program operations—reaching the target group in a cost-effective fashion. Monitoring may provide early warning signs that either program operations are faltering or that prevalence of micronutrient malnutrition is rising in one or more groups. Protocols for monitoring and evaluation must be developed as part of the overall program design and implemented as part of the program. Programs that have not done so have inevitably failed. Projects that have incorporated strong monitoring and evaluation components, such as the two programs promoting home gardens in Bangladesh described in Chapter 4 (see page 123), have been successful and have been sustained.

Indicators appropriate to monitor intervention impact will vary in accord with the intervention objective. For example, program objectives may be to improve coverage of iron-supplement recipients; to insure that a vitamin A-fortified food meets quality assurance standards or is selected for consumption by target groups; to cause a change in food consumption behaviors, such as the frequency of consumption of dark, green, leafy vegetables (DGLV); or to increase the year-round availability of vitamin A-rich food in household or community gardens. The appropriate intervention-specific *impact* indicator(s) for each of these objectives will differ; in some cases process indicators will be appropriate, and in other cases biological indicators will be the most useful. If the desired *outcome* of the intervention is to document a change in the vitamin A status of the recipient population, biological indicators are ideal. Use of impact indicators, however, can be limited in instances where they are difficult to measure and it is likely that a scaled-up intervention will not have the precision necessary to demonstrate impact. In such cases, process indicators should be substituted. For example, demonstrating that the target population received the supplement of vitamin A and ingested it is sufficient. Strong evidence is already available that vitamin A supplements reduce vitamin A deficiency and childhood mortality and morbidity; thus, it is not necessary to repeat these impact measurements.

Resource availability can limit the feasibility of direct biological evaluations because these indicators are usually more costly to obtain and evaluate than indirect indicator data. In such situations, outcomes derived from metabolic and/or controlled community studies lend credence to causative inferences from similar outcomes of interventions implemented in less rigorously controlled community studies. Inability to perform biological evaluations should not be the sole criterion that prevents initiation of, or stops, VAD control programs when and where such programs are needed.

Biological Indicators

Population monitoring of iron deficiency is difficult. Responsiveness of the left tail of an Hb distribution curve is probably the best and least expensive indicator of iron-deficiency anemia, but is inadequate to measure iron reserves. In spite of limitations noted in the background paper on iron, serum ferritin is likely to be the best indicator of measuring iron status. In developing countries with initial high prevalence rates of anemia (and hence prevalence rates of nearly 100 percent subclinical iron deficiency), however, assessing hemoglobin levels is enough.

VAD, like iron deficiency, is difficult to monitor. In the view of the workshop participants, process indicators can monitor most programs just as accurately as any single biological indicator and with less expense. Which to use depends on the mix of program strategies. Clinical indicators require very large

sample sizes because they are rare events. Night blindness is only useful in some populations and does not detect all subclinical VAD. The dynamic nature of the left tail of serum distribution curves among populations of young children is likely the best reflector for biological monitoring.

Monitoring of progress against iodine deficiency will usually involve both process and biological indicators. In a highly endemic area, goiter prevalence might be an appropriate initial indicator, but as a control program progresses, overall goiter rate is not an adequate indicator, because adult goiters are often fibrotic, and thus persist even when iodine deficiency is corrected. Goiter incidence in school-age children, however, could be appropriate until it becomes quite low. In contrast, median urinary iodine is reflective of current intakes of a population. Coverage can usually be monitored adequately—with least expense—by nonbiological process indicators such as the number of households in which iodized salt or other fortified food vehicle is consumed. To monitor quality control, however, quantitative laboratory methods for iodine levels in batches of salt, or median urinary iodine levels between cutoffs reflective of the desired level of iodine intake, are appropriate. Where the level of development favors institution-based deliveries, neonatal thyrotropin (TSH) —if a screening program for neonatal hyperthyroidism is already in place, as it is in much of Europe and other developed regions of the world—would be possible, but more expensive than urinary iodine. Median urinary iodine in representative school-age populations is likely the best indicator for long-term monitoring of iodine status and quality assurance of adequate salt iodization levels.

Background Papers

3

Prevention of Iron Deficiency

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Iron is an essential nutrient. Iron deficiency in humans has wide-ranging negative consequences, including impaired physical growth, compromised cognitive development, short attention span and impaired learning capacity, reduced muscle function and energy utilization, decreased physical activity and lower work productivity, lowered immunity, increased infectious disease risk, impaired fat absorption (most probably including fat-soluble vitamin A), increased lead absorption with all its negative consequences, and poorer pregnancy outcomes (Alaudin, 1986; Chandra, 1990; Dallman, 1974, 1986; Enwonwu, 1989; Husaini et al., 1990; Judisch et al., 1986; Li et al., 1994; Lozoff et al., 1992; Pollitt et al., 1982; Scrimshaw and SanGiovanni, 1997; Viteri and Torun, 1974; Walter, 1992). Iron deficiency also impairs the transformation of the thyroid hormones, T4 to T3, in peripheral tissues, the production and metabolism of epinephrine and norepinephrine, and leads to difficulty in maintaining body temperatures upon exposure to cold (Beard, 1990).

Functional consequences of severe iron-deficiency anemia during pregnancy include increased rates of premature delivery, perinatal complications in mother and newborn, low birthweight, low iron stores, and indications of iron deficiency and anemia in the newborn or in later infancy. Of great concern is the finding that some of the negative effects on cognitive and affective function of iron deficiency in infancy may persist, even after ion deficiency and anemia have been corrected (Lozoff et al., 1992). The majority of studies also report adverse consequences from mild to moderate iron deficiency and anemia.

The standard WHO criteria for anemia are shown in Table 3-1 (NSS1). These criteria indicate that the iron deficiency is of sufficient severity to interfere with hemoglobin formation, but iron has many other functions that are

more sensitive to iron depletion. Approximately 73 percent of the body's iron is normally incorporated into hemoglobin and 12 percent in the storage complexes ferritin and hemosiderin. A very important 15 percent, however, is incorporated into a variety of other iron-containing compounds essential to cell function.

WHO data indicate global rates for iron deficiency anemia in developing countries of 51 percent for children 0—4 years of age, 46 percent for school-age children, 42 percent for women, and 26 percent for men (NSS1) (see Table 3-1 for the WHO diagnostic criteria for iron-deficiency anemia). Even in the United States, the NHANES II survey found an overall 7 percent prevalence of actual anemia in women 15–44 years of age, but with the highest burden in minority and poverty groups (WHO/UNICEF/UNU, in press).

DIAGNOSIS OF IRON DEFICIENCY AND ANEMIA

In the absence of pathological iron losses, iron requirements are greatest during periods of growth (e.g., childhood); pregnancy; and, in women of reproductive age, because of menstruation. Documented associations between iron deficiency and ferropenic anemia include smaller babies, higher rates of stillbirth and perinatal mortality, more premature deliveries, and newborns with lower iron stores. An infant's risk of developing iron deficiency begins *in utero*, because premature delivery deprives the baby of the accumulation of iron near the end of pregnancy and smaller babies generally have less body iron (Widowson and Spray, 1951; Rosso, 1990). Unfortunately, the iron in breast milk cannot prevent the exhaustion of iron reserves in the first 4–6 months brought about by rapid growth. Poor weaning practices and inadequate feeding during childhood contribute further to the persistence or development of iron deficiency. When growth rates diminish, risk of iron deficiency is reduced unless there is abnormal blood loss to parasitic infection; menstruating women, however, continue to be at risk. In this group, about 20 percent have skewed menstrual blood (iron) losses in the upper ranges of the normal distribution that cannot be covered by their usual dietary intake, and over 50 percent have inadequate or depleted prepregnancy iron reserves (Cook et al., 1986; Custer et al., 1995; Franzetti et al., 1984; Hallberg and Rossander-Hulten, 1991). Because of the high iron requirements of pregnancy, iron deficiency is the rule, particularly in teenage gestations and in women with frequent pregnancies.

The stages in the development of iron deficiency are the depletion of iron stores, as indicated by low plasma ferritin; interference with biochemical processes, indicated by low transferrin saturation and elevated free erythrocyte protoporphyrin and serum transferrin receptors; and, finally, anemia, as indicated by low hemoglobin. It should be noted that although transferrin receptors appear promising as an indicator, standard cutoffs and interpretation of values from different commercial assays are yet to be developed. Up to an anemia prevalence

of 50 percent, the proportion of individuals with biochemical iron deficiency is about double those with actual anemia (WHO/UNICEF/UNU, in press). Above 50 percent, it can be assumed that nearly all of the population described is iron deficient. The significance of this finding is that these subclinical degrees of iron deficiency can interfere with cognitive, immune, and muscle function.

Pregnancy presents challenges in the diagnosis of both anemia and iron deficiency because of the normal and variable hemodilution, which lowers hemoglobin concentration to varying degrees, and the hormonal changes and the frequency of infection, both of which modify the indicators (Cook et al., 1994; Hytten, 1985; Puolakka et al., 1980; Romslo et al., 1983). Serum transferrin receptor levels appear especially useful in diagnosing iron deficiency in pregnancy (Carriaga et al., 1991). The lack of appropriate hemodilution in chronic undernutrition may mask the true level of anemia in the face of iron deficiency and decreased circulating hemoglobin mass (Rosso, 1990). Prepregnancy iron nutrition and hemoglobin level markedly influence the development of gestational anemia (Kauffer and Casanueva, 1990). There is thus a need to consider interventions that will improve prepregnancy iron reserves and provide extra amounts of iron, in addition to that in the diet, during gestation (Sloan et al., 1992; Viteri, 1994a,b, in press a,b).

After initial diagnosis of the prevalence of anemia and, ideally, the Hb distribution within a population, with emphasis on at-risk groups, the diagnosis of iron deficiency can be refined and verified by further biochemical tests. The Hb response to iron administration is best measured as part of ongoing surveillance of an adequate sample of the population. These additional steps could be implemented simultaneously. The surveillance system should be based on serial hemoglobin determinations in samples of population groups at risk (ideally also including serum ferritin) and periodic assessments at sentinel epidemiological sites.

TABLE 3-1 Cutoff Values for the Diagnosis of Anemia (WHO)

	Hemoglobin <		
Age/Gender Group	g/l	mmol/l	Hematocrit < l/l
Children			
6 months–5 years	110	6.83	0.33
5–11 years	115	7.13	0.34
12–14 years	120	7.45	0.36
Nonpregnant women (>15 years)	120	7.45	0.36
Pregnant women[a]	110	6.83	0.33
Men (• 15 years)	130	8.07	0.39

[a] The CDC proposes a cutoff point of 105 g/l during the second trimester. Severe anemia in pregnancy: Hb levels < 70 g/l; very severe anemia: < 40 g/l.

The general diagnosis of anemia should lead to a causal analysis. The necessary interventions and community participation toward the common aim of controlling iron deficiency and anemia must be the objective (WHO, 1991). The higher the anemia prevalence rates in a population, the greater the proportion arising from iron deficiency. There are also many different kinds of hemoglobinopathies, however; the most frequent is Hb-C, Hb-S and the thalassemias (alpha and beta; major, intermedia and minor, based on the degree of anemia they produce). The heterozygous A-S Hb affects up to 30 percent of some African populations (8 percent in African Americans). This genotype has essentially no hematological consequences, in contrast with the Hb S-S, which produces severe hemolytic and thrombotic crises (1 in 400 African Americans) and requires specialized medical attention. Hb-C produces mild anemia and affects about 4 percent of African Americans. The S-C Hb condition is associated with more severe anemia and is easily diagnosed. It affects about 1 in 850 African Americans. These hemoglobinopathies may explain failures of response to nutritional interventions in individuals, but they should not be a cause for modifying iron fortification or supplementation programs for populations at risk.

The thalassemias are a different problem because they produce anemia brought about by a failure in Hb production and chronic hemolysis. Children affected by thalassemia major generally have Hb levels below 60 g/l; those with thalassemia intermedia have Hb levels between 60 and 95 g/l, and those with thalassemia minor have Hb levels between 95 and 135 g/l. The more severe the anemia, the greater the stimulus to absorb iron and the greater the tendency to become iron-loaded, particularly because the only therapy customarily available for thalassemia anemia is repeated transfusions (justified only in thalassemia major or in special cases of thalassemia intermedia). The thalassemias are distributed primarily in populations of Mediterranean origin and of tropical or subtropical African, Middle Eastern, and Asian origin, generally areas where malaria has been endemic. In populations seriously affected by the thalassemias the concomitant iron deficiency of dietary and pathological origin (e.g., hookworm infection), as well as the risk of iron overload, must be evaluated and the programs adjusted accordingly (Charoenlarp et al., 1988).

Box 3-1 presents the suggested minimum information needed to make a tentative diagnosis of iron deficiency, estimate its public health significance, and plan the most appropriate interventions.

CAUSES OF IRON DEFICIENCY

Iron nutritional status depends on long-term iron balance. It is favored by the ingestion of sufficient iron in food (native, or added through fortification) in a bioavailable form or through iron supplementation. Regulation of iron absorption is crucial in favoring absorption in iron deficiency and in avoiding iron excess.

Balance is adversely affected by the amount of iron lost through gut mucosal turnover and skin desquamation; intestinal excretion; menstruation; the pregnancy-delivery-lactation cycle; and pathologic blood losses, mainly from excessive menstrual flow, hookworm and schistosomiasis, gastrointestinal bleeding from ulcerations, hemorrhoids, diarrhea, and other occult blood losses (Bothwell et al., 1979).

BOX 3-1 ANEMIA AND IRON DEFICIENCY AS A PROBLEM OF PUBLIC HEALTH IMPORTANCE: MINIMAL INDICATORS OF IRON DEFICIENCY (IN ORDER OF DECREASING RELIABILITY)

1. Anemia prevalence in the population: Iron deficiency is considered to be about 2 to 2.5 times the rate of anemia. This estimate applies when malaria is not endemic in the region and there are no reasons to suspect widespread hemoglobinopathies.

Category of public health significance	Prevalence of anemia in any at-risk group (%)
High	>20
Medium	12.0–19.9
Low	5.0–11.9

2. Records of anemia in health centers and clinics, as well as among hospital inpatient and outpatient pregnant women, women of childbearing age, and children between 6 and 36 months of age. If a categorization of severity is needed, the above-indicated prevalences would hold for these groups. For preschool-age children, schoolchildren, adolescents, and adult men, prevalences of 12 percent would be considered of "high public health significance." Any prevalence above 6 percent should be considered of public health significance in these groups.
3. Informed opinion of physicians or health personnel on the frequency of anemia (by measurement of Hb or Hct) or the presence of pale individuals (severe anemia), ideally individuals that have proved responsive to iron treatment.
4. A hemoglobin determination in 100-200 pregnant women at any time during the third trimester. Enroll clinics, hospitals, and traditional birth attendants. Use CDC cutoff values corrected for altitude.
5. Rapid survey of clinical paleness in vulnerable groups. Valid only if found in >5 percent of such groups. Negative surveys cannot rule out anemia as a problem.
6. Proxies:

- Hookworm infection is endemic.
- Vegetarian diets are followed by choice or because of food availability.
- Multiple pregnancies and teenage pregnancies.
- Data from neighboring areas or from areas of similar human and geoecological characteristics in the country or region.

In a healthy steady state, iron losses are fairly constant and iron balance depends mainly on the regulation of iron absorption: upward in iron deficiency and downward in iron sufficiency. The greater capacity to absorb iron in iron-deficiency situations is the most important short-term factor in the body's effort to maintain iron homeostasis. The amount of bioavailable iron in food is very important in the long term (Cook, 1990; Hulten et al., 1995).

There are no effective mechanisms for excreting the excess iron. Parenterally administered iron, including repeated blood transfusions, chronically excessive medicinal iron intake, or elevated iron absorption caused by impaired downward regulation of iron absorption (people homozygous for the hemochromatosis gene, some types of thalassemia, and hemosiderosis trait in some Black populations) lead to excess iron accumulation.

Food iron is present in most diets in a proportion of 6 mg/1,000 calories and is composed of two different pools: heme and nonheme iron (Hallberg and Bjorn-Rassmussen, 1972; Layrisse et al., 1969).

The heme iron pool includes all food compounds that have iron as part of heme molecules. Dietary heme iron is provided by animal blood, flesh, and viscera; the most important is hemoglobin in blood and myoglobin in muscle. In general, heme iron absorption is not modified by most inhibitors and enhancers of iron absorption. Exceptions are dietary protein, which increases heme iron absorption, and food calcium and manganese, which inhibit it. It must be clearly understood that these interactions occur while digestion and absorption of iron are taking place (within 2 hours of meal ingestion), and that only partial inhibition is produced by dairy products and other calcium-rich foods consumed in a varied meal, reducing iron absorption by 30 percent, at most (Gleerup et al., 1995; Hallberg et al., 1993). At the same time, heme iron absorption is also regulated upward and downward, but to a lesser extent than absorption of nonheme iron. In normal individuals, heme iron absorption fluctuates between 15 and 30 percent, but can increase up to about 50 percent in iron-deficient anemic subjects and can decrease to about 5–8 percent when the amount of heme iron is around 50 mg (Cook, 1990; Layrisse et al., 1973; Viteri et al., 1978).

The nonheme iron pool is made up of all other sources of iron. Nonheme iron is often bound in seeds, to phytic acid, and in other vegetable tissues to phenolic compounds. Nonheme iron is also present in heme-iron-containing and other animal tissues and in animal products such as milk and eggs. In contrast with heme iron, nonheme iron absorption is affected by many dietary components. Heme-iron-containing proteins and ascorbic, malic, tartaric, and succinic acids and some fermentation products are enhancers of nonheme iron uptake. Meat and alcohol also enhance nonheme iron absorption by promoting gastric acid production. Inhibitors include phytic acid and other polyphosphates, fibers, calcium, manganese, polyphenols such as tannins, and other compounds present in foods and beverages, especially tea, coffee, chocolate, and herbal infusions that produce polymers and insoluble, unabsorbable iron chelates.

Nonheme iron constitutes over 90–95 percent of dietary iron, particularly in the developing world. The absorption of nonheme iron can vary from 1 to 30 percent or more, depending on the presence of enhancers or inhibitors of absorption, and especially on the iron status of the individual (Bothwell et al., 1979; Cook, 1990; Layrisse et al., 1969). The latter is the most important factor in controlling iron absorption. In general, with meals of intermediate and high bioavailability, iron absorption can be as high as 5 mg of iron daily in iron deficiency. This is reduced to about 2–3 mg/day when diets are of poor bioavailability. As iron reserves increase, iron absorption decreases. When serum ferritin reaches 50–60 µg/l, equivalent to about 500 mg of iron reserves, iron absorption from daily meals of intermediate and high iron bioavailability allows the absorption of only about 1 mg of food iron/day, which is equivalent to the replacement of average obligatory losses, not including menstruation (Hulten et al., 1995). There is no published information of this kind for daily meals with poor bioavailability, but extrapolations suggest that this amount of iron would be absorbed with iron reserves of only about 140 mg.

Cook (1990) has also summarized the importance of iron nutritional status on heme and nonheme iron absorption in a single meal containing both kinds of iron (see Table 3-2). The percentage of heme and nonheme iron absorbed increased by a multiple of 2.4 to 8.4 among iron-deficient, compared with normal, men. If the meal contained only nonheme iron, the percentage of absorption would be reduced to one-half that presented in Table 3-2.

Several important conclusions can be derived from the above:

- Dietary composition appears to be particularly important when iron reserves are low or in the presence of iron deficiency.
- Downward regulation of iron absorption is very effective, even when the diet is rich in heme iron and of a composition that favors iron absorption. Therefore, the development of iron-overload conditions from dietary iron intake in normal individuals is highly improbable.
- Poor-quality diets would not satisfy the iron needs of a large percentage of menstruating women and would not allow the accumulation of iron reserves beyond about 150 mg, which is below the ideal for women entering pregnancy.

TABLE 3-2 Percentage of Iron Absorption

Source of Iron	Normal Men	Normal Women	Iron-Deficient Subjects
Heme	20	31	47
Nonheme	2.5	7.5	21

SOURCE: Cook, 1990.

For simplicity, diets have been classified as of high, intermediate, and low bioavailability, depending on the proportion of heme iron and the presence of inhibitors and enhancers of nonheme iron absorption. Their respective bioavailabilities have been averaged at 15, 10, and 5 percent, respectively. A woman of childbearing age with requirements of absorbed iron at the median of 1.25 mg/day, and consuming a diet of poor bioavailability, would need to ingest 25 mg of iron in order to achieve adequate intake. This would mean that she would have to ingest 4,170 calories daily of an average diet containing 6 mg of iron/1,000 cal compared with an average energy intake of 2,100 cal/day by this population. If the diet is of intermediate (10 percent) bioavailability, only 50 percent of women would be able to maintain a normal iron status and about 20 percent would develop anemia. Only a very small proportion would be able to build adequate iron reserves for pregnancy. The majority of these women would rapidly develop iron deficiency and gestational anemia during pregnancy.

Most of the iron compounds used for the fortification of foods become part of the nonheme dietary iron pool, and their absorption is similar to that of the other components of the pool and subject to inhibitors and enhancers (Bothwell et al., 1979). Exceptions to this rule are soluble iron chelates, which are 2 to 5 times more efficiently absorbed than the dietary nonheme iron pool in the presence of inhibitors, and purified bovine Hb, which becomes part of the heme-iron pool when used as a fortificant. The bioavailability of soil iron, which contaminates many staples and vegetables, is largely unknown, although it is generally considered low.

The absorption of iron compounds administered as 30–120 mg boluses for supplementation or therapeutic purposes presents a different picture. When given without food, absorption declines logarithmically with logarithmic dose increments, but it remains at about 6 to 8 percent, even after apparent repletion of iron stores, possibly because of mass action (Bothwell et al., 1979; Grebe et al., 1975; Hallberg and Sölvell, 1967; Viteri et al., 1978). Svanberg (1975), however, found only 2 percent absorption of supplemental iron in late pregnancy. This steady absorption from large doses of iron explains why, in mg of iron absorbed, higher iron intakes allow higher, but less efficient, iron absorption.

Animal studies have demonstrated that iron absorption is particularly inefficient when supplemental or therapeutic iron is administered at short intervals (several times a day, daily, or even every 2 or 3 days). This "mucosal block" to iron absorption caused by repeated iron administration has been well documented in several animal species (Fairweather-Tait et al., 1985; Hahn et al., 1943; Stewart et al., 1950; Viteri et al., 1995a; Wright and Southon, 1990).

In humans, the absorption data are not as clear, but they suggest that for less than 1 week of daily iron supplementation, or even with 2 to 4 daily doses, the blockage is minor, if it operates at all, among nonanemic and normal or mildly iron-deficient subjects (Cook and Reddy, 1995; Höglund, 1969; Norrby, 1974;

O'Neil-Cutting and Crosby, 1987; Reizenstein et al., 1975;. Rush et al., 1966; Smith and Pannacciulli, 1958; Solomons, 1995). Iron blockage in the human under different iron nutritional conditions has not been fully explored. In a detailed study by Hallberg (1970), the absorption efficiency of administering 37 or 74 mg up to 4 times a day was highly variable. On average, iron absorption was around 8–9 percent.

Finally, in considering iron regulation and metabolism with the aim of preventing iron deficiency, interactions with other nutrients are important in their effect on the absorption and utilization of iron. Copper is involved in oxidoreduction of iron in the process of absorption, transport, storage, and mobilization; folate and vitamin B12 are involved in nucleic acid synthesis of all cells and clearly in erythropoiesis, thus modifying iron utilization; vitamins B6 and B2 are specifically required in the process of heme synthesis; and amino acids are required for protein synthesis in general, and for hemoglobin synthesis in particular. Vitamin A is involved in mobilization of iron reserves, in Hb synthesis, and appears to favor iron absorption in the presence of inhibitors (Hodges, et al., 1978; Layrisse et al., 1997; Mejia et al., 1979).

Low dietary iron intakes—particularly where much of the iron is in non-heme form—combined with the increased iron needs of growth or pregnancy, and even the small chronic iron losses of mildly excessive menstrual flow, increase the risk of developing iron deficiency and anemia. These risks are often further exacerbated in developing countries by parasitic infections. Endemic malaria increases the prevalence and aggravates the severity of anemia, particularly among young children and pregnant women, and produces iron sequestration and some iron losses (Brabin, 1992). As with other hemolytic processes, folate and vitamin B12 requirements are also elevated by malaria (Fleming, 1990). Hookworm disease is a serious cause of intestinal blood loss (Layrisse and Roche, 1964; Roche and Layrisse, 1966). Infection with *Schistosomia haematobium* causes blood loss in the urine and can result in intestinal bleeding (Scrimshaw et al., 1968).

IRON EXCESS

Objections to the strategies for the control of iron deficiency have sometimes been raised by hematologists in developed countries. They cite the danger of possibly accelerating or inducing iron excess and overload conditions in some clinical conditions, as well as claims for its involvement in a variety of cancers and heart disease in their countries (Halliwell et al., 1992; Herbert, 1992; Lauffer, 1992; Stevens et al., 1994). These issues cannot be ignored in this paper. Nevertheless, in the face of the widespread iron deficiency and ferropenic anemia in the great majority of populations in the developing world and in groups at risk for iron deficiency everywhere, this should not be an issue (ACC/SCN, 1997; Gillespie, 1996) as long as monitoring of interventions is in place to avoid

excessive administration of iron in therapeutic and chronic supplementation programs (a minimal requirement in any nutrition intervention program). Food iron (including that included in iron-fortified food) poses no threat to these populations.

The recessive genetic disorder, hemochromatosis, is particularly prevalent in white populations of European descent, especially those of Celtic origin. Regions with particular haplotypes have been identified in central Sweden and in northeast Italy. In the U.S. Caucasian population, the homozygous state is never less than 0.1 percent and may be as much as 0.5 percent in some population groups (Lynch, 1995). Hemochromatosis exists at a possible rate of about 1 percent among African-Americans, but its etiology needs further clarification (Wurapa et al., 1996). A recent preliminary report by the Centers for Disease Control and Prevention (CDC) indicates that a prevalence among Hispanics in San Diego, California, is similar to that seen among non-Hispanic American whites (CDC, 1996). The consequences of iron excess are mainly liver cirrhosis and increased liver cancer. Heart failure from myocardial dysfunction and diabetes brought about by pancreatic disease are suggested rare consequences, but this remains highly controversial (Lynch, 1995).

The adoption of general iron fortification of foods in the developing world, where iron deficiency is highly prevalent, has been slowed further by fears of accelerating iron overload conditions in genetically prone individuals, even though this is a relatively rare clinical problem. It is not a reason to withhold the benefits of iron fortification as a public health measure from the overwhelming majority of the population (Ballott et al., 1989a). This fear has been based on concern in industrial countries, where iron deficiency is less of a problem.

PREVENTION OF IRON DEFICIENCY IN AT-RISK GROUPS

Control measures for iron deficiency and anemia should not be considered in isolation, but rather as part of integrated approaches to combat micronutrient malnutrition and within the general objectives of alleviating critical poverty; achieving sustainable food security; and improving the economic, health, overall nutritional, and educational status of the population. This obvious statement is emphasized to stress that no single approach to dealing with iron deficiency and anemia will work for all populations and in all settings. The approach taken in this paper is to evaluate successful interventions for iron from a lifestyle perspective. Table 3-3 presents a summary of successful interventions that, based on experience, can be implemented in the short, medium or long term for different categories of target individuals. The implementation of medium- and long-term strategies can be accelerated under favorable circumstances. Once established, process and impact evaluations should be performed periodically within a defined surveillance system to determine if there is a need for continuation, modification, or even suspension of a given strategy.

Infancy

The first preventive measure against infant iron deficiency is assuring adequate body iron at birth by avoiding gestational iron deficiency and other conditions leading to low birthweight and premature delivery (Colomer et al., 1990; De Benaze et al., 1989; Puolakka et al., 1980; Scholl and Hediger, 1994; Scholl et al., 1992). The importance of prepregnancy iron nutrition in preventing gestational iron deficiency has not been sufficiently recognized.

Current intrauterine devices (IUD) increase menstrual flow in many women (INACG, 1981), but IUDs can be effectively used in combination with some form of iron supplementation.

Birth spacing and delaying pregnancy beyond the teen years allow the deposition or recovery of iron reserves after the pubertal growth spurt or a previous pregnancy (Beard, 1994; Bothwell et al., 1979; INACG, 1981).

A second critical measure for improving the iron stores of the newborn is delayed ligation of the umbilical cord. Ligation of the umbilical cord after it stops pulsating (about 30–60 seconds after delivery) increases the infant's blood volume about 60 ml, providing approximately 34 mg of iron, which equates to between 25 and 30 percent of the newborn's total circulating iron (Burman, 1969; Lanzkowsky, 1976). These additional 34 mg of iron are equivalent to what a healthy, exclusively breast-fed baby would absorb in 5 months. In theory, this delayed ligation will determine whether a 6-month infant is iron deficient or not.

In the first 4–6 months, breast-feeding is an important contribution to the maintenance of better iron nutrition in infants. Research has clearly shown that exclusively breast-fed infants have greater iron stores than infants who are formula-fed (Saarinen et al., 1977). The amount of iron in human milk is very small (< 0.6 mg/l), and its bioavailability, once thought to be around 50 percent (McMillan et al., 1976; Saarinen et al., 1977), has recently been shown to average 11 percent (Davidsson et al., 1994 a,b). Even though exclusively breast-fed infants generally enter into iron deficit after about 6 months, their non-breast-fed counterparts are usually iron deficient sooner. The universal promotion of exclusive breast-feeding for 4 to 6 months is thus a key element in maintaining adequate iron nutriture.

Infants beyond about 6 months of age need an additional source of iron beyond that provided by breast milk. A large body of evidence documents that iron deficiency and anemia in older infants and young children can be prevented by appropriate complementary feeding. When breast-feeding is not possible, iron-fortified milk preparations are needed (Walter et al., 1990, 1993a).

Another alternative after about 6 months of age is preventive iron supplementation. In this age group, once iron deficiency is present, anemia develops quickly and therapy with oral iron is needed to rapidly improve the infant's hematological status and avoid possible permanent developmental deficits. The

TABLE 3-3 Strategies for Improving Iron Status

Strategy	Infants	Preschool Children	School-Age and Pubertal Children	Pregnant and Lactating Women	Nonpregnant Women
Short-term	Gestational iron status Exclusive breast-feeding for 4–6 months; Delayed cord ligation Preventive iron supplementation Parasite and malaria control where needed After 6 months, periodic deworming where needed	Preventive iron supplementation Parasite and malaria control where needed Periodic deworming where needed	Preventive iron supplementation Parasite and malaria control where needed Periodic deworming where needed General vitamin and mineral fortification in school-feeding programs	Iron and folate supplementation Breast-feeding Parasite and malaria control where needed Deworming where needed	Birth spacing Avoiding nonsteroidal IUDs Parasite and malaria control where needed Periodic deworming where needed Preventive iron supplementation
Medium-term	Improved sanitation and hygiene Iron-fortified milk and weaning products General iron fortification	Improved sanitation and hygiene Targeted fortification General iron fortification	Improved sanitation and hygiene Targeted fortification General iron fortification	Improved sanitation and hygiene General iron fortification	Improved sanitation and hygiene General iron fortification

Long-term	Improved sanitation and hygiene Improve complementary feeding, including heme-iron-containing foods	Improved sanitation and hygiene Diet diversity Total food intake	Improved sanitation and hygiene Diet diversity Total food intake	Improved sanitation and hygiene Diet diversity Total food intake	Improved sanitation and hygiene Income improvement Diet diversity Total food intake

NOTE: Parasite and malaria control measures should continue through the medium and long terms; for specifics, consult WHO/UNICEF/UNU (in press).

strategy of iron supplementation for this age group is often neglected by those who are unaware that the vast majority of infants live in poor households in the developing world, where the resources for preparing highly bioavailable, iron-rich foods complementary to breast-feeding or for purchasing iron-fortified foods are nonexistent. The risk associated with iron deficiency at this age is so serious that even in the United States, the American Academy of Pediatrics (1992) and the Institute of Medicine (1993) recommend that supplementary iron of 1 mg/kg/day should be provided to infants, and that the dose should be doubled for preterm infants, not to exceed 15 mg/day (a total of 105 mg/week). In preterm infants, supplementation should also start earlier, usually by 2 months of age, but very low birthweight infants should receive supplements as early as 3 weeks of age, provided that vitamin E intake is adequate (Fomon and Zlotkin, 1992).

DeMaeyer (in WHO, 1989), the ACC/SCN (1991), the World Bank (1994), and WHO/UNICEF/UNU (in press) have all emphasized the importance of making supplements available to infants where they are at risk of iron deficiency.

Preschool Children (3 to <7 Years of Age)

The rapid growth of the early years exacerbates the need for iron, and young children are particularly at risk of iron deficiency and anemia. This is true in both developed and developing countries. A number of studies have demonstrated that if anemia is mild to moderate and iron supplements are administered at proper doses, anemia correction can be achieved in a few months.

Iron therapy is intended to correct anemia quickly and uses high iron doses, while preventive iron supplementation aims at improving iron nutrition over a longer period of time and with lower doses and fewer side effects. Therefore, they differ in purpose, iron dose and frequency, and duration of intervention (Gillespie, 1996; INACG, in press). Lack of clarity in this differentiation has led to confusion and has delayed the acceptance of the prevention of iron deficiency through supplementation administered on a weekly basis, as discussed below. At present, the only short-term measures suggested by WHO for the control of iron deficiency are the treatment of those already anemic and periodic repeated administration of daily iron supplementation among populations that exhibit high prevalences of anemia, with the purpose of keeping anemia rates under control (DeMaeyer, 1989).

The alternative of continuous preventive supplementation by a weekly dose was first explored by Liu et al. (1995a,b), who studied 246 kindergarten children, ages 3 to 6, in the city of Changji in China. This investigation compared the effect of daily and weekly iron supplementation on iron nutrition by studying all of the children, whether or not they were iron deficient or anemic. In that population, 39 percent of the children were iron deficient (serum ferritin <20

µg/l) and 16 percent had very low serum ferritins (<12 µg/l); 37 percent of the children were anemic (Hb less than 110 g/l). Children were randomly assigned to 3 months of directly supervised iron supplementation. They were divided among daily, biweekly, and weekly supplementation, with three age-determined classroom groups in each regimen (nine classrooms in total). Each iron regimen provided 6 mg of elemental iron/kg per dose. This is a therapeutic level, equivalent to 120 mg of elemental iron in an adult (about 10 times the normal daily requirement). Results indicate that anemic children (Hb < 110 g/l) responded to all three supplementation regimens with an increase of 10 g Hb/l or more. There were no anemic children left at the end of any of the supplementation regimens studied. In addition, 31 percent of the nonanemic children also increased their Hb levels by at least this amount. Serum ferritin increased significantly in all three groups. Those most deficient in Hb and ferritin showed the greatest response, as would be expected. This study indicated that there was no need to administer more than 6 mg of iron/kg weekly to correct anemia characterized by Hb levels < 110 g/l and > 80 g/l and establish adequate iron stores.

The difference in side effects among the three regimens was dramatic. Among the daily dose group, 35.4 and 39.7 percent of anemics and nonanemics, respectively, reported some side effects—anorexia, nausea, some vomiting, diarrhea, constipation, and abdominal discomfort. Among the children receiving the iron twice weekly, 7.4 percent of anemics and 6.6 percent of nonanemics reported side effects. Anemic and nonanemic children receiving weekly doses presented 0 and 5.7 percent side effects, respectively. The authors conclude that the amount of iron absorbed by these children from weekly doses of 6 mg/kg was enough to prevent iron deficiency and to eliminate anemia in the course of three months. The biweekly and weekly regimens had far fewer reported side effects than the program of daily dosing.

Schultink et al. (1995), in anemic Indonesian preschool children receiving daily or twice-weekly iron at a dose of 30 mg, demonstrated that both regimes were equally effective in correcting the anemia in 8 weeks. In Bolivia, Berger et al. (1997) achieved similar results by administering 3–4 mg of iron/kg daily or weekly for 4 months to 4- to 7-year-old anemic children.

Intestinal parasitosis, and hookworm in particular, is a significant contributor to iron deficiency in older infants and preschoolers in many developing countries (Stephenson, 1987; Stolzfus et al., 1997). Chronic fecal blood loss from infection with hookworm in this age group has been recognized as an important cause of severe iron deficiency and anemia for years in many parts of the world (Bloch, 1971, 1986). Malaria and parasite control measures (including treatment of those affected) should be implemented for this age group where these conditions are endemic (Warren et al., 1993).

School-Age Children and Adolescents

As in the case of preschool children, no specific short-term measures are currently used for the continuous prevention and control of iron deficiency in these vulnerable populations. Periodic cycles of daily iron supplements and treatment of those who are already anemic, plus periodic deworming, are recommended by WHO (WHO/UNICEF/UNU, in press).

In Chile, the use of bovine hemoglobin concentrate to fortify cookies for schoolchildren met with success (Hertrampf et al., 1990; INACG, 1986; Stekel, 1984; Walter et al., 1993b). This program was extensively evaluated and proved that it could effectively prevent iron deficiency and increase iron reserves in menstruating adolescent girls attending school, reducing the proportion of girls with serum ferritin < 20 µg/l from 33 to 17 percent. Unfortunately, the cost of this fortification process is relatively high. In Guatemala, iron intake has been improved in the school population (boys and girls from 6 to 18 years of age) by the daily distribution of high-energy, high-protein cookies, fortified with a multivitamin and multimineral mix (INCAP, 1984). Unfortunately, there has not been a systematic evaluation of the effect of this intervention on iron status or anemia prevalence.

The effectiveness of weekly 60 mg iron + 0.25 mg folate doses has been demonstrated in Malaysia by Tee et al. (1995). The doses were administered by teachers for 5 months (a total of 22 tablets) to adolescent schoolgirls, anemic or not, in correcting mild to moderate anemia and improving iron reserves. In this double-blind study, a nonanemic control group that received only folate did not improve in iron nutrition.

The most comprehensive study of the impact of hookworm on anemia in schoolchildren in general, and its effect on iron status and iron-deficiency anemia, was reported recently by Stoltzfus et al. (1997). In populations in which hookworm is a public health problem, hookworm eradication could reduce anemias. Its impact is greatest among the severely infected children, who also have the most severe iron deficiency and anemia. A major challenge is to ensure the prevention of reinfection by repeated deworming, plus adequate fecal waste disposal and the wearing of closed shoes. Effective, safe, and inexpensive anti-helminthic drugs are now available and their use has accelerated the control of hookworm infection (WHO, 1995).

Women of Childbearing Age

Although in many developing countries 30–60 percent of menstruating women are victims of iron-deficiency anemia, and in some countries nearly all are iron deficient, little attention has been given to this group in planning and implementing specific control measures. These women receive attention only

when they become pregnant. Yet pregnancy is only a part of the reproductive cycle that starts prior to pregnancy and ends only at the end of lactation. It is well-established that their iron nutritional status during pregnancy will be assured only if women enter pregnancy with adequate iron reserves (<300 mg of iron reserves). Nevertheless, women are often grossly neglected as social and productive members of families and societies; they suffer all the consequences of iron deficiency and anemia, whether or not they are pregnant (e.g., Li et al., 1994).

Only recently has attention been given to menstruating women as targets for iron supplementation. In the United States, an ad hoc expert panel on iron deficiency in women of childbearing age recommended that nonpregnant women be treated with 60 to 180 mg of iron/day if they are found anemic and their serum ferritin levels < 20 µg/l (Anderson, 1991). Treatment and maintenance doses (30 mg/d) should continue until serum ferritin reaches 40 µg/l at 6- and 12-month evaluations. The panel recognized that the risk of anemia during pregnancy is greater among women who enter pregnancy with depleted iron stores and recommended universal iron supplementation during gestation as a prophylactic measure. They stress that special attention should be given to groups at greater risk: multiparous and adolescent women who have low-income, less than a high school education, are Black or Mexican Americans, and are blood donors. Similarly, Sloan et al. (1992) conclude from their analysis of multiple iron supplementation trials that "it is difficult to treat a severely iron-deficient woman and provide for increased fetal needs through iron supplementation during the relatively short period of pregnancy." They state that "as a public health approach, prolonged supplementation beginning *before* the woman becomes pregnant may be a better strategy to benefit the majority of the population (although some individuals will always require more aggressive treatment)."

Two published studies confirm the efficacy of weekly iron supplementation of nonpregnant women of reproductive age. In Indonesia, 273 girls with an anemia prevalence of 17.5 percent were divided into four groups (Angeles-Agdeppa et al., 1997). Group 1 received 60 mg of Fe, 750 ug retinol, 250 ug folic acid, and 60 mg. ascorbic acid. Groups 2 and 3 received 60 mg or 120 mg of Fe weekly plus 6,000 µg retinol, 500 ug folic acid, and 60 mg. ascorbic acid. Group 4 received only a placebo. After two months of supervised intake and a further three months of unsupervised intake, the increase in hemoglobin was the same in all three groups receiving iron and declined in the placebo group. With 60 mg weekly, the incidence of GI side effects was 5.7 percent, the same as in the placebo group, compared with 32.8 percent when 60 mg were given daily. The rise in ferritin at 3 months was highest in the daily supplemented group and intermediate in the weekly groups. Six months after the last supplement, however, the daily and weekly groups had the same ferritin levels, and these were in the normal range.

A 7-month, double-blind, unsupervised study was conducted in Berkeley, California, to compare 7 months of weekly with 3 months of daily iron supplementation (as recommended by WHO) in correcting iron deficiency and building iron reserves in healthy women of child-bearing age. Supplements were consumed daily in Phase I, lasting 3 months, and weekly in Phase II, lasting 4 months, by three randomized groups: Group 1 (N = 37) received daily iron + folate tablets (60 mg of iron as $FeSO_4$ and 250 µg folic acid) during Phase I and weekly folate tablets (250 µg folic acid) during Phase II; Group 2 (N = 35) received a folate tablet 6 days and an iron + folate tablet 1 day every week in Phase I and one weekly iron + folate tablet during Phase II; Group 3 (N = 44) received only folate tablets during both phases. Overall adherence among those completing the study was over 90 percent. Side effects were given as important reasons for withdrawal from the study and were highest with daily iron. At baseline, between 11 and 16 percent of the subjects were iron deficient, and between 8 and 16 percent had low Hb levels, depending on the ferritin (<12 or <15 µg/l) and Hb (<120 or 125 g/l) "cutoffs" used. Ferritin levels during Phase I significantly increased only in Group 1 ($p < .001$); however, during Phase II, Group 1's ferritin levels fell back to baseline levels ($p < .001$), whereas Group 2 sustained a moderate increase, especially during Phase II ($p < .05$ vs. baseline of same group). Group 3's ferritin levels remained stable throughout the two phases. Mean Hb levels were not different among the three groups. However, the proportion of women with Hb < 125 g/l in Group 1 decreased in Phase I but returned to baseline proportion in Phase II; this proportion showed a sustained decrement in Group 2 throughout both phases and showed no specific tendency in Group 3. Iron supplementation by 30 doses administered weekly over 7 months was as effective as or even more effective than as 90 does consumed daily only during the first 3 months.

For women of childbearing age in the developing world, WHO (DeMaeyer, 1989) and a multiagency consultation (WHO/UNICEF/UNU, in press) indicate that for preventive purposes, adolescents and adult women should receive a 2- to 4-month course of 60 mg of iron daily. This course should be repeated every year, or when needed to deal with anemia. This recommendation has been largely ignored, and this regimen can now be replaced by weekly iron supplementation for as long as the women are at risk.

Pregnant Women

The regulation of iron metabolism in pregnancy is unique, because profound hormonal changes, functional adaptations, and large increments in iron requirements occur during this time. Iron absorption increases as pregnancy advances (Barrett et al., 1994; Hahn et al., 1951; Heinrich, 1970; Svanberg, 1975; Whittaker et al., 1991). The mechanism most often suggested is the increase

in red-cell mass and total blood volume, but the progressive development of iron deficiency and other metabolic adaptations during this physiologic state (e.g., increasing plasma transferrin and erythropoietin levels and high levels of placental transferrin receptors) must also play a role.

The physiologic hemodilution that leads to normal decrements in hemoglobin concentration further complicates the evaluation of iron supplementation in pregnancy. Moreover, the reported lack of anemia among chronically undernourished women because of their reduced capacity to expand their plasma volume introduces another variable that is sometimes difficult to control (Rosso and Streeter, 1979; Rosso et al., 1983). Women who enter pregnancy with iron deficiency and low Hb levels will respond to iron administration (a therapeutic effect), but their final Hb levels may still be abnormally low (e.g., Sood et al., 1975). Even in healthy, apparently well-nourished women, Hb falls progressively. Many women develop anemia from the second trimester onward. Hb concentration usually reaches its lowest concentration by 20–28 weeks gestation, and many of the women who develop anemia remain anemic after delivery (Hytten and Duncan, 1956). Iron supplementation of pregnant women has been viewed as the main global strategy for controlling iron deficiency and anemia.

The evaluation of the effectiveness of iron supplementation based on increments in Hb without controlling for initial iron status, Hb levels, and gestational period is fraught with possible errors. Moreover, pregnancy is physiologically an inopportune time to correct prepregnancy iron deficiency because of the elevated iron requirements during the last two gestational trimesters (Scholl and Hediger, 1994; Viteri, 1997a,b). A combination of Hb, plasma or serum ferritin, and transferrin receptor levels is appropriate for the evaluation of interventions during pregnancy (Carriaga et al., 1991; Skikne et al., 1990).

Because of the dual demands for growth and reproduction, pregnant teenagers are at particular risk (Osofsky, et al., 1971). Birth spacing can thus be an effective preventative measure for the control of iron deficiency in teens and adult women. Epidemiological data confirm that multiparous women are more at risk of becoming iron deficient and anemic (Andrade et al., 1991; Pilch and Senti, 1984). Multiparity is associated with larger menstrual flows, and thus with greater chronic iron losses (Andrade et al., 1991). Lactation and its accompanying amenorrhea favors a positive iron balance during the postpartum period, and hormonal contraceptives reduce menstrual flow by one-half (Cole et al., 1971).

In both developed and developing countries, iron supplementation is routinely recommended as part of antenatal care. In the United States, the Food and Nutrition Board of the National Academy of Sciences (1990) recommends the daily use of 30 mg of elemental iron after the twelfth week of pregnancy. Pregnant women with anemia, associated with low serum ferritin, should receive treatment with daily iron at doses of 60–120 mg to restore Hb to normality. When this is achieved, the woman should receive 30 mg of iron daily. The Institute of Medicine (IOM, 1990, 1993) recommended universal supplementation

with 30 mg of iron daily during the third trimester only if the pregnant woman's Hb is <110 g/l. In the second trimester, providing 30 mg of iron daily is recommended if the woman had serum ferritin levels <20 µg/l, even if she was not anemic. In the first trimester the same scheme applied, but supplementation was expanded to cover women with mild anemia (Hb 90–109 g/l).

The most recently published statement from WHO (DeMaeyer, 1989), which was directed to the developing world, recommended universal iron supplementation for pregnant women (60 mg of elemental iron and 250 µg of folic acid, once or twice daily) through the primary health care system. The twice-daily regimen was recommended where gestational anemia was common (most of the developing world). The conclusion of published studies in both the developed and developing world is that the greatest benefits to mothers and infants are achieved when iron deficiency and anemia are controlled as early as possible in pregnancy with doses that do not surpass 60 mg daily.

The review of iron nutrition during pregnancy performed by the Institute of Medicine (IOM, 1990) confirms the relative inefficiency of administering large iron doses to women in industrial countries to improve Hb levels at the 35th–40th gestational week. In effect, the maximal mean Hb concentration at term (127 g/l) was achieved by daily ingestion of either 200 mg of sustained-release iron (Puolakka et al., 1980; Svanberg, 1975) or 65 mg of iron (Taylor et al., 1982), and the maximal mean difference was only 3 g/l, compared with a ferrous fumarate supplement providing 30 mg of iron/day (Chanarin and Rothman, 1971). Moreover, Chanarin and Rothman (1971) compared the relative efficacy of administering supplements of 30, 60, and 120 mg of iron/d for 24 weeks on Hb concentration at term, and found no significant differences among the three regimens.

As demonstrated by the proportion of women who reach the end of pregnancy with Hb levels reaching the accepted cutoff of 110 g/l, short-term iron supplementation of already iron-deficient and anemic pregnant women is very inefficient, even with large daily iron doses (Charoenlarp et al., 1988; Hahn et al., 1951; Simmons et al., 1993; Sood et al., 1975; Svanberg, 1975). These studies confirm that administering high doses of iron not only results in over 90 percent of the iron remaining unabsorbed in the gut, but also produces undesirable side effects in exponential proportion to the iron dose (Hallberg et al., 1966; Sölvell, 1970). Sloan et al. (1992) conclude from their analysis of multiple iron supplementation trials that "it is difficult to treat a severely iron-deficient woman and provide for increased fetal needs through iron supplementation alone during the relatively short period of pregnancy." They suggest that "as a public health approach, prolonged supplementation beginning *before* the woman becomes pregnant may be a better strategy to benefit the majority of the population."

While the great majority of developing countries recommend iron supplementation during pregnancy, the programs have not been particularly effective because of logistic and compliance problems. Two recently completed studies, one in China (Liu et al., 1995a) and the other in Guatemala (Chew et al., 1996),

demonstrate that weekly iron administration to pregnant women under direct supervision is efficacious. In China the study involved 416 primiparous pregnant women older than 20 years. Anemia prevalence was 33 percent by mid-pregnancy and 20 percent at term, whether they received 60 or 120 mg of iron daily or 120 mg weekly. There were no differences by supplementation schedule and dose in either initial or final Hb and ferritin values. A negative control group had initial anemia prevalence of 20 percent, which became 47 percent at term, and serum ferritin showed a drop from 30 to 17 µg/l.

In the Guatemala study, involving 383 women, prevalence of anemia was 27 percent at about mid-pregnancy, and 16 percent, 25 percent, and 33 percent at term for supervised 60 mg daily and 180 mg weekly, and the group under usual care, respectively. In this population, which was significantly more iron deficient than the Chinese women studied, 60 mg daily supplementation resulted in a greater increase in Hb than 180 mg weekly. This is the only study to date in which the results of daily and weekly supplementation have not been the same for the effect on hemoglobin levels. Nevertheless, no women in either of the groups ended with a Hb value below 95 g/l, indicating that daily and weekly iron supplementation were both effective in reducing risks.

Current evidence indicates that the absorption of supplemental iron is lower in multivitamin and multimineral antenatal supplements than when it is administered alone. This is because of the presence of high levels of calcium and magnesium (Babior et al., 1985; Seligman et al., 1983). The administration of iron supplements with meals decreases their absorbability by about 50 percent (Layrisse et al., 1973; Reizenstein et al., 1975). In improved absorption, delayed release preparations are promising (Cook et al., 1990). The evidence is strong that a blockage of absorption of zinc and copper is a consequence of daily intake of iron in amounts that elevate the ratio of iron to zinc above 2 and that of copper above 20–40:1 (Breskin et al., 1983; Burns and Patterson, 1993; Dallman, 1990; Hambidge et al., 1987; Solomons, 1986; Solomons and Jacobs, 1981; Walsh et al., 1994). A study by Reizenstein et al. (1975) suggests that food-iron absorption is also reduced in the face of supplemental iron intake.

According to the meta-analysis performed by Mohamed and Hytten (1989), iron administration during pregnancy among well-nourished pregnant women did not have a significant beneficial effect on proteinuric hypertension, antepartum hemorrhage, maternal infection, short gestation, or low birthweight. These last results agree with those of Higgins et al. (1982) and contrast with those of Garn et al. (1981), Murphy et al. (1986), Scholl et al. (1992), and Scholl and Hediger (1994), who have clearly shown short gestation or low birthweight with anemia and iron deficiency at mid-pregnancy or before. Anemia and iron deficiency at mid-pregnancy or earlier are more critical than they will be at term in inducing preterm delivery and low birthweight. This fact may partially explain some conflicting results derived from late iron supplementation among mildly iron-deficient populations in the developed world. The controversy in demonstrating

a beneficial effect of correcting mild to moderate anemia in preventing abnormalities during pregnancy as well as in improving newborn weight and overall health in the developed world contrasts with the results in the developing world, where severe anemia is common and consistent differences in the above parameters are documented between more anemic and less anemic or normal women. A re-analysis of the data in the Indian study by Sood et al. (1975) (cited by Mohamed and Hytten, 1989) shows that iron supplementation among poorly nourished, pregnant Indian women reduced anemia prevalence and severity at term, as well as low birthweight, with an odds ratio of 0.31 (0.17–0.56). Several earlier and later papers from India (Rusia et al., 1995, 1996) have also shown functional and placental morphologic alternations and changes in newborn status among iron-deficient, anemic pregnant women. Agarwal et al. (1991) also showed a marked reduction in low birthweight babies (odds ratio: 0.54) in the supplemented compared with the control group. In this study, the percentage of low birthweight babies (weight < 2,500 g) was reduced from 37.9 among the control group to 23.1 among women supplemented with iron from the 20th to 24th week to term, and to 12.1 among those supplemented from the 16th to the 19th week to term. It is important to point out that among the 137 iron-supplemented women, only 1 had an Hb level below 101 g/l at term (0.7 percent), in contrast with the control group, where 33 percent of women had lower Hb levels.

There is also clear evidence that infants born to mothers who received iron supplements during gestation had better iron nutrition and more than twice the iron reserve at 2 months of age and beyond when compared with their counterparts whose mothers were not given iron supplements (De Benaze, 1989; Puolakka et al., 1980). Children born to iron-deficient, anemic mothers have a significantly higher risk of having anemia or iron-deficient erythropoiesis at 1 year of age, as defined by an odds ratio of 7.6, with 95 percent confidence limits of 1.9–11.2 (Colomer et al., 1990).

Nevertheless, in a meta-analysis of iron administration during pregnancy among well-nourished pregnant women by Mohamed and Hytten (1989) and in a paper by Higgins et al. (1982), it did not have a significant beneficial effect on proteinuric hypertension, antepartum hemorrhage, maternal infection, short gestation, or low birthweight. This has led to doubts about the risk associated with mildly anemic pregnant women as defined by the Hb cutoff to label a pregnant woman as anemic (110 g/l according to WHO). There is a general consensus, however, based on solid evidence, that risk is significantly elevated with Hb levels < 90 g/l (Danforth, 1982; Duthie et al., 1991; Sloan et al., 1992).

The beneficial effect of the administration of folic acid in addition to iron during pregnancy has been amply demonstrated in many parts of the world (Chanarin and Rothman, 1971; Fleming, 1990; Sood et al., 1975; Velez et al., 1966; Viteri, 1973). The effect of iron supplementation may be reduced by other nutrient deficiencies. Where vitamin A deficiency is endemic, even if not clinically

apparent, the administration of vitamin A in combination with iron and folic acid produces a greater improvement in the hematological status of pregnant women at term than iron alone (Suharno et al., 1992, 1993). Powers et al. (1985) reported an additional effect of iron supplementation with vitamin B2 in The Gambia, where the deficiency of this vitamin is endemic.

Even mild hookworm infections can be devastating to women of childbearing age, particularly to pregnant women because of their already high iron requirements. A recent WHO consultation (1995) concluded that given the safety of the new deworming drugs, "single-dose, oral anthelminthic treatment can also be given to pregnant and lactating women. However, as a general rule, no drug should be given in the first trimester." The effect of deworming on pregnant women (Atukorala et al., 1994) was clear; women receiving iron supplements and deworming medication (Mebendazole) showed better hematological responses than those receiving only supplements. The supplement tablets contained 60 mg of elemental iron and 0.25 mg of folic acid, and women were instructed to take 1, 2, or 3 tablets daily for 8–26 weeks. The number of tablets ingested, based on a questionnaire, made no difference in hematological or biochemical parameters. Duration of supplementation did: the women supplemented for > 17 weeks responded better.

SUSTAINABLE APPROACHES TO THE ELIMINATION OF IRON DEFICIENCY

Dietary Improvement

There is a general consensus that the most desirable, sustainable, and safest strategy for the control of iron deficiency is the sustained ingestion of bioavailable iron in food in adequate amounts and reducing iron losses throughout the life cycle. Three main approaches are recognized; a discussion is provided below.

Improving the Supply and Intake of Food Iron

It has been recognized that the availability of food iron has lagged behind that of energy and protein achieved by the enhanced production and true availability of staple foods (FAO, *Food Balance Sheets*, 1961–1988). The per capita availability of leguminous seeds (an important source of iron for many regions) has been declining sharply (FAO AGROSTAT/PC, 1992), and the intake of heme iron from meat, fowl, and fish in the developing world has, at best, remained stationary, at a very low level. Unfortunately, green leafy vegetables are generally poor sources of dietary iron because of its low bioavailability in these sources, although some are rich in this mineral.

There are many vegetables that are good sources of iron and vitamin C, and the identification and promotion of their use in combinations that favor nonheme

iron absorption should be undertaken by agricultural extension agencies, nutrition personnel, and community groups, particularly in the developing world and in cultures where vegetarianism is common. A balanced vegetable diet can maintain an adequate iron status and avoid anemia, even in women and children, as exemplified by studies of well-informed, Western vegetarian groups, such as the Seventh Day Adventists (Dwyer, 1988; Sanders, 1994). Nevertheless, the prevalence of iron deficiency and anemia in Asian vegetarian populations and in the populations of the developing world that are mainly vegetarian by economic necessity are significantly higher than in otherwise similar omnivore populations (Craig, 1994; Shaw et al., 1995). The inclusion of unfermented soy products in a diet reduces iron bioavailability (Cook et al., 1981).

Improving the Bioavailability of Food Iron

Extensive research, summarized by the International Nutritional Anemia Consultative Group (INACG, 1982) and Hallberg et al. (1992), identified the influence of food components and meal preparation on iron bioavailability. The key issues are reducing the ingestion of inhibitors to iron absorption and increasing the intake of enhancers in a given meal. These include germination of seeds; heat treatment of cereals; fermentation processes; higher intake of meats and of foods and beverages that contain vitamin C; and increasing the intake of acid sauces (e.g., tomato sauces). Others are improving the intake of vitamin A-rich foods, especially preformed vitamin A; cooking vegetables rich in vitamin C sparingly, and cooking cereals, seeds, and the like that are rich in phytates more intensively. The intake of inhibitors can be reduced by decreasing the consumption of high-fiber, high-phytate, and high-polyphenol foods such as tea, coffee, chocolate, and herb teas and separating the intake of high-calcium foods and supplements from iron-rich meals. Educating people about food choices, dietary combinations, cooking practices, and intrahousehold distribution strategies that improve iron supply and bioavailability in each meal is a neglected strategy.

Agricultural research into the production of new genetic varieties of cereals with reduced inhibitor (e.g., phytic acid) content, and thus more bioavailable iron, is promising (Combs et al., 1996). Most of these varieties are still in the agronomic and genetic experimental stages, but some are already the subject of studies in humans (Mendoza et al., in press). It is too early to project these results to population groups. Research on the importance of certain green leafy vegetables as a source of bioavailable iron is urgently needed, because there is currently not enough information to evaluate the effectiveness of their contribution to improving iron nutrition (de Pee et al., 1996).

Correcting other nutrient deficiencies that may alter iron absorption and metabolism through dietary changes is also a worthwhile measure. Special attention should be given to ensuring adequate vitamin A, folate, riboflavin, and vitamin B12 nutritional status. Unfortunately, the best food sources of these

nutrients, except for folate, are animal products, including milk and its products, eggs, meats, and viscera, many of which are out of reach for populations with limited resources or who live far from markets and cannot engage in the production of small livestock and poultry. The best sources of folate are organ meats, green leafy vegetables and sprouts, and some fruits (including oranges, cantaloupes, and melons). Folate can be lost by prolonged cooking in large volumes of water. It is estimated that between 50 and 90 percent of food folate is destroyed during cooking.

The favorable dietary practices previously described must be learned and utilized by food providers, preparers, and those responsible for the distribution of food in the household. Empowerment of communities is essential in achieving the desired dietary practices. Different approaches to communication and education in food and nutrition (e.g., social marketing, reflexive participation, and so forth) are only part of this process, which will be lengthy if it is to be sustainable. This is particularly important since the effects of improving iron nutrition (increasing iron reserves and/or reducing anemia prevalence and incidence) can only be perceived after many months or years and because increments in total dietary iron absorption are moderate (Hulten et al., 1995).

Food Fortification

Iron fortification of foods is a preventive measure that aims at improving and sustaining iron nutrition on a permanent basis (Bauernfeind and Lachance, 1991). It can be targeted to groups at risk of iron deficiency or to whole populations, depending on the characteristics of their diet, the epidemiology of iron deficiency and other nutritional anemias, the availability of appropriate iron compounds and food vehicles, the available industrial and logistical facilities, and the financial resources, among other considerations. Fortification of foods can include only iron (single fortification), or it can be extended to encompass two or more nutrients (multiple fortification). It can use a variety of iron compounds and vehicles. A number of recent publications address this food-based strategy in detail (Bothwell and MacPhail, 1992; Clydesdale and Wiemer, 1985; Cook and Reusser, 1983; Hurrell, 1984, 1985, 1992, in press). For fortification of any kind to be effective, three essential factors are necessary: (1) an effective and affordable iron compound must be available and acceptable; (2) a food vehicle must also be available and accessible; and (3) detailed production instructions and monitoring procedures must be in place and enforced by law.

A variety of foods have been used for iron fortification. Ideally, the food selected is consumed regularly in sufficient, stable quantities by the target populations and is centrally processed, easy to fortify, stable in storage, inelastic to price, minimally altered by the addition of the fortificant, and amenable to proper regulation and monitoring. The food that is used also needs to be priced so that an increment in cost of the fortified product, including packaging, can be

absorbed by the population, the government, the producer, or the retailer, or in some combination of these groups.

Fortification Compounds

The iron preparations used in the fortification of a variety of food products can be categorized in four main groups (Hurrell et al., 1989):

1. Water-soluble compounds, such as $FeSO_4$ and ferrous gluconate, are inexpensive but have a metallic taste and are reactive, leading over time to oxidation products and off-flavors and colors. Nevertheless, for products with rapid turnover, they are usually the fortificants of choice. Microencapsulation can extend shelf life, but increases price.
2. Poorly water-soluble compounds, soluble in dilute acid solutions, can be used. Ferrous fumarate, succinate, and saccharate belong to this category. Because they are less reactive, they are preferred for fortifying semisolid or solid foods, such as infant cereals and food powders, but they are more expensive.
3. Water-insoluble compounds, poorly soluble in acid solutions, including the phosphate salts (ferric orthophosphate, pyrophosphate, and ferric-ammonium orthophosphate) and forms of elemental iron (reduced, carbonyl, and electrolytic irons), belong in this group. These compounds are stable, poorly reactive, and essentially tasteless, but they are generally poorly and unpredictably absorbed, depending on the manufacturing processes. Heating of the fortified product can improve the bioavailability of these compounds. Ferric-ammonium orthophosphate has a significantly better absorbability.
4. Chelated iron compounds, such as bovine hemoglobin concentrate, FeNaEDTA, and amino-acid chelates are soluble in water. FeNaEDTA has the advantage of being stable and without flavor. An important characteristic of iron chelated with EDTA is that it enhances the absorption of the whole nonhemeiron pool (INACG, 1993; Viteri et al., 1978). EDTA itself (for example, FeNaEDTA, CaNaEDTA, or NA2EDTA), at a molar ratio to nonheme iron • 1, also enhances iron absorption by a factor of approximately 3 or 4 (MacPhail et al., 1994). Bovine Hb concentrate has a definite taste, requires a strong sanitary infrastructure, and is more reactive than FeNaEDTA. It is very effective as a fortificant, however, and also improves the absorption of dietary nonheme iron (Stekel, 1984; Walter et al., 1993b). Its higher cost is partly compensated by its much higher absorption.

The iron content, relative bioavailability in the rat and the human, enhanced absorption achieved by addition of vitamin C to fortified cereals, and approximate relative cost of the most common iron sources for food fortification are presented in Table 3-4.

Fortification Strategies

Many industrial countries and some developing countries fortify a cereal product. Fish sauce, sugar, and curry powder have also been successfully used as vehicles for iron fortification with NaFeEDTA in Thailand, Guatemala, and South Africa, respectively (Ballot et al., 1989a,b; Garby and Areekul, 1974; Viteri et al., 1983; 1995b). Amino-acid chelates are being tested for their effect on anemia prevalence and ferritin levels in feeding trials in Brazil and other countries. These include cheeses and wheat and maize flours fortified with low levels of iron (to provide about 2 mg/d). Results appear very promising (Bovell-Benjamin et al., 1997; Olivares et al., 1997; Pineda, 1996).

Many industrial countries have fortified milk and soy-based formulas with different iron compounds (ferrous sulfate, ferric ammonium citrate, and ferric or sodium iron pyrophosphates) for consumption by infants and young children (Bothwell and MacPhail, 1992; Fomon, 1987; Theuer, 1985). Most formulas are currently fortified with ferrous sulfate (12 mg of iron/l), with the addition of 55 mg of vitamin C. Several studies in Chile have also demonstrated the effectiveness of iron fortification of cow's milk with ferrous sulfate alone, or with ascorbic acid (INACG, 1986; Stekel, 1984).

Cereal-milk infant and weaning foods have also been fortified with about 100–120 mg of insoluble iron compounds/kg for many years, but the bioavailability of such iron compounds is generally poor (Rios et al., 1975). Nevertheless, the consumption of 16 mg of iron/day from a rice cereal fortified with 550 mg of electrolytic iron /kg was effective in preventing iron deficiency and anemia in Chilean infants (Walter et al., 1993a). These results are encouraging industry to add water-soluble or poorly water-soluble/acid-soluble iron compounds together with ascorbic acid to prepared infant foods (Cook and Reusser, 1983; Hurrell et al., 1989). Formulated protein mixtures intended for infants and preschool children—such as INCAPARINA, COLOMBIARINA, BIENESTARINA, and many others—including rations for refugee populations, are also fortified with iron, mostly as ferrous sulfate. Rice-based weaning foods have been successfully fortified with bovine hemoglobin concentrate (Calvo et al., 1989).

Complementary foods and a variety of cookies used in school feeding programs are being fortified with iron and other nutrients in different countries. The short shelf life of these products makes it possible to use the relatively inexpensive ferrous sulfate. In Chile, the use of bovine hemoglobin concentrate to fortify cookies for schoolchildren has been successful (Hertrampf et al., 1990; INACG, 1986; Walter et al., 1993b). This program effectively prevented iron deficiency and increased iron reserves in menstruating adolescent girls attending school, reducing the proportion of girls with serum ferritin < 20 µg/l from 33 to 17 percent.

TABLE 3-4 Characteristics of Iron Sources Commonly Used to Fortify Foods

Iron Source	Approximate Iron Content	Average Relative Bioavailability			Approximate Relative Cost	
		Rat[a]	Man[a]	+ Vitamin C[b]	A[c]	B[d]
Freely water-soluble						
Ferrous sulfate 7H2O	20	100	100	×3.7	1.0	1.0
Dried ferrous sulfate	33	100	100	—	0.7	0.7
Ferrous gluconate	12	97	89	—	5.1	5.7
Ferrous lactate	19	—	106	—	4.1	3.9
Ferric ammonium citrate	18	107	—	×12.9	2.1	—
Poorly water-soluble/soluble in dilute acid						
Ferrous fumarate	33	95	100	—	1.3	1.3
Ferrous succinate	35	119	92	—	4.1	4.4
Ferric saccharate	10	92	74	—	5.2	7.0
Water-insoluble/poorly soluble in dilute acid						
Ferric orthophosphate	28	6–46	25–32	×4.0	4.1	16.4–12.8
Ferric ammonium orthophosphate (EKA Nobel, Sweden)	19	—	45–58	—	2.3	5.1–4.0
Ferric pyrophosphate	25	45–58	21–74	—	2.3	11.0–3.1
Elemental iron powders						
Electrolytic	98	44–48	5–100	×2.4	0.5	10.0–0.5
Carbonyl	98	39–66	5–20	—	1.0	20.0–5.0
Reduced	97	24–54	13–148	—	0.2	1.5–0.14

Chelated compounds						
Gastric delivery system (Ferrous sulfate)						
NaFeEDTA - 3 H2O	14	—	100–416[e]	×2.1	6.0	6.0–1.4[f]
Amino-chelated iron (Albion)	26	—	100–500[g]	—	—	—
Concentrated bovine hemoglobin	0.34	—	100–700	—	30.0	6.0[f]

[a] Relative to FeSO4-7H2O = 100, at the same level of total iron.
[b] Relative increase in absorption when vitamin C is added to cereal products.
[c] Relative to FeSO4-7H2O = 1/mg Fe.
[d] Relative to FeSO4-7H2O iron actually absorbed = 1/mg Fe.
[e] At proper doses (1 molar ratio EDTA/Fe • 1).
[f] Cost per mg total Fe absorbed may be even lower because of higher total nonheme dietary iron absorption.
[g] Preliminary.
SOURCE: Bothwell and MacPhail, 1992; Bovell-Benjamin et al., 1997; Cook and Reusser, 1983; Forbes et al., 1989; Hurrell, 1985, 1992, 1997; Hurrell et al., 1989; Olivares et al., 1997; Viteri et al., 1978; Walter et al., 1993.

Effectiveness of Iron Fortification

Many studies involving large groups of subjects have been carried out to evaluate the impact of a given iron fortification strategy on anemia and iron nutrition (Cook and Reusser, 1983; Dutra de Oliveira et al., 1996; Fomon, 1987; Hurrell, 1997; Indian Council of Medical Research, 1989; Viteri et al., 1995b). Despite the long history of cereal fortification in industrial countries, there are almost no studies confirming its effectiveness for reducing iron deficiency. The majority of studies have involved infants and children, where the impact of iron-fortified formulas, milk and soy preparations, and infant foods has been amply documented. The experience of these trials can be summarized by indicating that iron deficiency and anemia in older infants (8 months and older) and young preschool-age children can be essentially eradicated by the consumption of iron-fortified milk preparations after 4 to 6 months of exclusive breast-feeding, by the consumption of iron-fortified infant foods, or both. Even when breast-feeding is not possible, the consumption of fortified formula is efficacious. Vitamin C is an important additive in these preparations (Dallman, 1986; Filer, 1989; INACG, 1986).

There are five large studies in developing countries that address the effectiveness of general iron fortification, one each in Thailand, India, South Africa, Guatemala, and Venezuela (Ballot et al., 1989a; Garby and Areekul, 1974; Layrisse et al., 1996; Viteri et al., 1983, 1995b; Working Group on Fortification of Salt with Iron, 1982) (see the Appendix, p. 83). These five studies provide reassuring examples of the effectiveness of general iron fortification of foods when it is based on careful planning and well-established guidelines. A study of a province in Argentina (Tierra del Fuego) is in progress involving iron-fortified milk with microencapsulated ferrous sulfate, recommended especially for consumption by children and pregnant and lactating women (A. O'Donnel and E. Carmuega, personal communication, 1996), and two large projects involving fortification of corn tortillas and sugar with multiple nutrients is ongoing in Mexico (A. Chavez, International Life Sciences Institute (ILSI) *ILSI News*, December, 1996).

These studies also demonstrate that:

- Many different sources of iron and the vehicles employed can be effective in raising the iron intake of populations to levels that could not be achieved by diet alone, unless dramatic changes took place in food patterns. For example, it would be almost impossible to raise the iron intake of the average Indian citizen by 10 to 15 mg/d. It would require doubling or tripling the current dietary intake.
- Significantly raising the intake of nonheme iron, even though its absorption is low, can markedly improve the status of iron-deficient populations.

- Significant changes, compared with groups with no intervention, occur rather quickly in such populations, but slow down as iron nutrition improves and iron stores increase. Therefore, the full effect of fortification requires a long time.
- With rare exceptions, iron fortification of foods does not affect the iron status of populations that are well nourished in iron. This implies that the risk of iron overload from iron fortification in normal individuals is essentially nil, and that probably only in the long term will the iron reserves of menstruating women reach the levels needed to reduce the risk of iron deficiency in pregnancy.
- The use of chelated iron as NaFeEDTA has demonstrated advantages: it is well absorbed, it promotes dietary nonheme iron absorption in the face of inhibitors, it improves zinc absorption and nutrition, and it does not appear to affect the absorption of calcium or copper. The use of amino-acid-chelated iron appears promising.
- Double fortification of sugar with microencapsulated retinyl palmitate and NaFeEDTA is possible and effective. Equally possible is the double fortification of salt with iron and iodine, now done in some Indian states, but problems with the stability of iodine in salt still prevail. Multiple fortification of flours and specially prepared foods can also be effective (for example, maize and wheat flours fortified with ferrous fumarate and cookies fortified with Hb or multivitamin and multimineral mixes).

Iron Supplementation

During Pregnancy

A synthesis of iron supplementation trials prior to 1956 and up to 1983 (Hytten and Duncan, 1956; Mohamed and Hytten, 1989) and an exhaustive review of studies from 1966 to 1989 (Sloan et al., 1992) indicate that iron administration during pregnancy drastically reduced the prevalence of Hb values < 100–105 g/l (odds ratio 0.12, 95 percent confidence interval 0.07–0.20). The mean Hb change in the combined studies was positively related to duration of supplementation, and the lower the Hb before supplementation, the greater its positive change, as would be expected. In the absence of iron supplementation, pregnancy was generally associated with declines in hemoglobin. Iron administration during pregnancy also reduced the prevalence of serum ferritin values <10 µ/l at 36–40 weeks gestation in relation to unsupplemented women (odds ratio 0.05, 95 percent confidence interval 0.02–0.11).

Given the clear benefit of iron supplementation during pregnancy to both mother and child among populations where iron deficiency is a serious public health problem, why has this intervention not had more success in reaching the

target audience? There are a number of reasons: lack of political will and program support; inadequate awareness of the seriousness and magnitude of the problem; lack of clarity in differentiating iron deficiency and anemia; poor compliance with taking the iron supplements—in part, because of the side effects—and low coverage of at-risk populations.

The lack of political will and program support in Latin America are clearly evident from a survey of programs in 38 countries by Viteri (1996) and the reports of two subregional workshops covering all Latin American countries (Gueri and Viteri, 1996; Viteri et al., 1996b). Opinions on the relationship between noncompliance with iron supplementation and reported side effects vary. Studies conducted in Africa, Asia, the English-speaking Caribbean, Latin America, and the western Pacific vary in the level of side effects reported (ACC/SCN, 1991; Charoenlarp et al., 1988; Chew et al., 1996; Ekstrom et. al., 1996; Liu et al., 1995a; Ridwan et. al., 1996; Simmons et. al., 1993; Viteri, 1996). Adherence to supplemental programs can be improved by information, education, and motivation at the community level, including explanations of the possible temporary discomforts secondary to iron intake. Flexibility in dose to reduce side effects; in the rigidity of daily intake; in the time the supplement is taken (with meals or at bedtime, rather than between meals during the day); and other modifications according to culture, knowledge, practices, and attitudes also improve adherence (ACC/SCN, 1991). With weekly dosage, side effects were lessened in infants (Husaini, 1996), preschool children (Liu et al., 1995b), and pregnant women (Chew et al., 1996; Liu et al., 1995a).

Lack of adequate coverage of the target populations has been an equally important reason for the poor success of iron supplementation interventions. Current practices of iron supplementation rely almost exclusively on the health care system. Lack of commitment on the part of medical and other health personnel, inadequate operation of the health system, insufficient and inconsistent supplies of the needed supplements, and difficulty gaining access to medical facilities are all reasons that have been given for low coverage rates of pregnant women. Other reasons, frequently ignored, are that people simply forget to take the supplement, particularly if no clear benefit is evident. There are also misconceptions about the effect of supplements (e.g., sterilization, big babies with more difficult labor, and the like).

As with many other public health measures, the key to success is involvement of all levels of the community from the inception of the program and active community participation in its operation, evaluation, and in implementing the modifications that are necessary based on rapid-evaluation feedback. This requires the informed delegation of authority from the health system to the community. The former should establish efficient information and monitoring systems to ensure the efficiency and safety of the programs and to actively seek integration of efforts both within and outside the health system, including the cooperation of community resources (for example, schoolteachers, religious and

civic leaders, industrial and commercial organizations, mother and infant clubs, AA, and the like).

Prepregnancy Supplementation

If a woman enters pregnancy with adequate iron stores, she has a higher probability of going through pregnancy and the full reproductive cycle without developing iron deficiency. Preventive supplementation of women of childbearing age before and after pregnancy, through repeated reproductive cycles, offers the best potential for reducing iron deficiency.

The historical development of iron supplementation programs and general efforts to control iron deficiency have suffered from several factors:

- Iron deficiency has no evident and dramatic health effects until it is extremely severe, although its hidden functional and health effects may be more widespread and equally important in their detrimental effects on individual, social, and economic development and well-being. Even the 40 percent of maternal deaths that are associated with severe anemia (hematocrit < 14 percent in young teenagers) have been often ignored, except for acute emergency treatment (Harrison and Rossiter, 1985). Overall association of severe anemia and maternal deaths was about 20 percent in India (Menon, 1968) and as high as 50 percent in severely anemic Nigerian women (Fullerton and Turner, 1962).
- The factors that influence adherence and rejection of current iron supplementation programs have been given inadequate analysis and attention. Failure of programs has been attributed mainly to attributes of the recipients and the characteristics of the medication; little attention has been given to the operational difficulties of daily antenatal supplementation.
- Prepregnancy iron reserves have not received adequate attention, and their importance has often been ignored, even among the leaders in the field of iron nutrition. Initial Hb level is the strongest predictor of Hb level at term, and prepregnancy serum ferritin is an important predictor. The value of entering pregnancy with iron reserves has been well demonstrated (Kauffer and Casanueva, 1990), can be easily understood, and is clearly recommended by two papers (Sloan et al., 1992; WHO/UNICEF/UNU, in press), but it is not mentioned in many major declarations regarding iron supplementation in pregnancy or in important reviews of the subject.
- There has been confusion about the meaning of "physiologic anemia of pregnancy" in both well-nourished populations in industrial countries and in poorly nourished populations in developing countries. In the industrial world, Hb levels at term at the lower limit of normality or in the upper end of the "anemia" range (100g/l) are of no consequence; they may even appear beneficial in many cases (Mohamed and Hytten, 1989). In the developing world, many chronically undernourished women are incapable of fully expanding

plasma volume (Rosso, 1990). Consequently, the true deficit in Hb mass from anemia is masked, and even mild anemia is pathological under these circumstances.

- Limiting the implementation period for measures to correct iron deficiency and anemia to the last half of pregnancy is far from ideal, particularly if large doses of daily iron are recommended, because of the unpleasant side effects produced in a significant proportion of women. In many places there has been no other choice, because iron supplementation has depended exclusively on the health system and pregnancy has been the only time when health centers have contact with women.
- The "medicinal," high-iron-dose approach has faced many problems, including increased dose-related side effects, having to ingest several tablets a day, and logistic and motivational problems among providers (ACC/SCN, 1991; Galloway and McGuire, 1994). Furthermore, it has tended to limit the practice of iron supplementation to the health system. Unfortunately, this system works very poorly in many countries, and it is essentially unavailable to over half of the rural population in the developing world (UNDP, 1991).
- Even though every study shows that unsupplemented women have lower Hb levels and display clear indications of iron depletion at term when compared with supplemented women, confusion arises because supplemental iron intake should be planned primarily to *prevent* iron deficiency and an abnormal fall in Hb. Increments in Hb are to be expected only among women who are already anemic on first evaluation, but initial Hb level is the strongest predictor of Hb level at term (Baker and DeMaeyer, 1979; Charoenlarp et al., 1988; Chew et al., 1996; Liu et al., 1995a; Ridwan et al., 1996; Sood et al., 1975).
- Hb concentration at term is also subject to the level of plasma expansion. In the therapy of ferropenic anemia, the rate and the magnitude of the Hb response to iron intake is proportional to the initial Hb deficit and is, up to a point, modified by the supply of iron, among several factors. It appears that duration of supplementation is more important than dose; the earlier iron supplementation starts, the more effective it is (Atukorala et al., 1994; Charoenlarp et al., 1988; Sloan et al., 1992).

As a response to these issues, "preventive supplementation" based on a community-centered regimen of weekly iron doses to populations or groups within populations at risk of developing iron deficiency has been proposed (Viteri 1993, 1994b, 1995). This proposal originated from animal studies showing that synchronizing the administration of iron supplements with the turnover of the intestinal mucosa improved the efficiency of iron absorption by a factor of more than 2.5 (Viteri et al., 1995a) and by the results of a pilot study in preschool children in China by Liu et al. (1995b). The latter demonstrated equally satisfactory results in improving hemoglobin status after 3 months of supplying 6 mg of iron/kg in daily, twice-weekly, and weekly iron supplementation.

The theoretical basis for the weekly schedule in the human is that intestinal mucosal turnover occurs every 5 to 6 days.

The International Iron Nutrition Project (IINP) of the United Nations University (UNU), in cooperation with WHO and UNICEF, and with the financial support of various donor agencies—Micronutrient Initiative (MI), International Development Research Centres (IDRC), IMPACT/AID—initiated comparative studies of the efficacy of weekly iron in field studies covering a number of population groups, from infants to pregnant and childbearing-age women. Stimulated by the protocol, a number of independent studies have also been completed. Ten studies in which consumption of each supplements is supervised have now been completed in women and children in Bolivia, China, Guatemala, Indonesia, Malaysia, and the United States (ACC/SCN, 1997). The results published to date are given in the section on Prevention of Iron Deficiency in At-Risk Groups. They indicate that at an appropriate dosage, and with assured compliance, hemoglobin levels are the same after 2 to 3 months with both daily and weekly regimens unless there are complicating factors such as malaria. The potential logistic and financial advantages of a weekly supplement compared with daily dosage are obvious. The challenge is to demonstrate the practicality of large-scale weekly programs with sustainable mechanisms to ensure adequate compliance.

Based on these results, women of childbearing age with low iron reserves (at risk of iron deficiency and anemia) can take a tablet containing 60 mg of iron + 3.5 mg of folic acid on a weekly basis, before going to bed, as an established routine supported by community organizations under the direction and monitoring of the health sector. Several studies now indicate the safety and efficacy of this dosage. An average of 8 percent of that iron is expected to be absorbed in iron replete subjects (Cook and Reddy, 1995), providing the equivalent of 0.7 mg of iron daily. Absorption may be as high as 40 percent or more in iron-deficient anemic subjects, providing the equivalent of 3.8 mg/day. The long-term effect would be to correct iron deficiency and increase iron reserves to desired levels (currently found in only 50 percent of women of childbearing age in the United States—Cook et al., 1986—and few women in most developing countries). Women should be encouraged to double the dose as soon as they are found to be pregnant. After delivery they could go back to the single, weekly dose.

BENEFITS AND COSTS OF PREVENTING IRON DEFICIENCY

Table 3-5, modified from WHO/UNICEF/UNU (in press), presents the estimates of relative effectiveness and cost per Disability Adjusted Life Year (DALY) of different supplementation strategies and offers a comparison with iron fortification computed by various models (Murray and Lopez, 1994).

Community-based preventive supplementation through widespread weekly iron supplements that cover all subjects at risk of iron deficiency and anemia is estimated to have a relative cost 1.5 times the cost per DALY in the case of universal iron fortification plus weekly residual prenatal iron supplementation. Current practice of only daily prenatal iron supplementation is estimated to be 6.25 times more expensive per DALY than the estimate for community-based, preventive weekly supplementation. In addition, the number of DALYs achieved in the short-term with either widespread preventive iron supplementation or universal fortification multiplied by the average yearly income of the population that benefits from such programs, divided by the estimated cost of the intervention ($24,00 or $16,000), represents the respective benefit/cost ratio. Based on UNDP average yearly income figures (US$241.5), adjusted by the proportion of the work force that stands to benefit from the control of iron deficiency and anemia, benefit/cost ratios are 46.9 and 81.4, respectively. This ratio increases further when the long-term benefits are considered and the medium- to long-term reduction in costs of treatment of anemia are taken into account.

TABLE 3-5 Cost and Benefit/Cost Ratios of Iron Supplementation Schemes and General Iron Fortification Programs

Intervention	Benefit/Cost Intervention	Number of DALYs[a] Achieved	Cost per DALY (US$)
Short-term (daily, weekly) benefits and costs of iron supplementation programs			
Prenatal supplementation only	511	100	51
Widespread supplementation to all iron-deficient and anemic subjects and at-risk groups	4,665	88	24
Universal fortification	5,038	16	11
Plus residual prenatal supplement[b]	5,394	39	16
Long-term benefits and costs of iron supplementation programs			
Preventive supplementation	2,679	37	17
Fortification	3,332	9	

[a] Per 100,000 population, considering global birth rates, fixed and other operational costs, and current individual expenditures in purchasing iron-containing preparations (based on information from Guatemala).

[b] Considering that in spite of iron fortification and adequate prepregnancy iron reserves, prophylactic iron supplementation will still be recommended during pregnancy.

Prevention of Iron Loss Due to Parasites

Many recent reviews have been written on the problem of intestinal parasitosis, hookworm in particular (Stephenson, 1987; Stolzfus et al., 1997a,b; Warren et al., 1993; WHO, 1995). The chronic fecal blood loss from infection with hookworm has been recognized as a cause of iron deficiency and anemia for many years (Layrisse and Roche, 1964; Roche and Layrisse, 1966; Scrimshaw et al., 1968). Eliminating hookworm infection by adequate fecal waste disposal and the wearing of shoes is the best solution. As an immediate intervention, deworming, especially the effective prevention of reinfection, is an important intervention in the control of iron deficiency and anemia among male tropical agricultural workers.

A significant advance in the availability of effective, inexpensive, essentially unabsorbable and safe anthelmintic drugs in recent years has allowed the acceleration of the control of hookworm infection by repeated anthelmintic medication. Costs of deworming are difficult to calculate, because most estimates of cost are based on health system interventions, which are expensive, and costs to prevent reinfection are not considered. For example, a school nurse who rotates among schools could direct and supervise interventions at the schools at a cost of about US$2.00 per pupil yearly. One dose of albendazole costs about US$0.15. Given the safety and efficacy against hookworms of the drugs being used now, community-based programs should be implemented. This would reduce the costs. Deworming has many other advantages in addition to decreasing iron losses, so that benefit/cost ratios are favorable. Data on costs and benefit/cost ratios are urgently needed. Even World Bank documents (Warren et al., 1993) do not have specific data on the costs of treating hookworm infection.

SUGGESTED NATIONAL GOALS

There is no reason to delay actions to control iron deficiency among populations at risk, particularly those in the developing world. The evidence is over-whelming that iron deficiency and anemia have serious negative effects.

Short-Term

1. Each country should draw up a plan of action that will lead to the following medium- and long-term goals:

- The 5-year, medium-term goal: Reduce to one-third the current prevalence estimates of anemia in pregnant women and children from 9 months

of age to school-age and improve prepregnancy iron nutrition and antenatal supplementation practices.

- The 10-year, long-term goal: Eradicate nutritional anemia and iron deficiency as a public health problem, defined as not more than 5 percent ferropenic anemia in each age and gender group at risk of iron deficiency. This would mean not more than 10 percent iron deficiency in each age and gender group at risk.

2. Each country should determine which of the possible interventions available to prevent and correct iron deficiency and anemia, and their combinations, are most suitable to implement and/or improve immediately. These should include the adoption of the concept that pregnancy is a part of the life of mature women, and that it should not be considered in isolation. The chosen plan of action, including the suitable interventions, should be coordinated with efforts to control vitamin A deficiency and other nutritional and relevant health problems that impinge on the iron nutritional situation of the population, with emphasis on the pregnant and lactating woman, early childhood, and women of childbearing age.
3. Each country and the international community should implement mechanisms for national and international decisionmakers to become aware of the extent and severity of the problem; to be informed of the existing options for the control of iron deficiency and anemia, including benefit/cost ratios; and to be sensitized to take action. International and bilateral agencies, nongovernmental organizations, and other donor agencies must be prepared to assist governments that are willing to act.
4. Each country should establish national and local groups to promote the programs. The group will include technical members in government and academic institutions, as well as leaders from both within and outside the community who will develop a sense of ownership of the campaign to control iron deficiency and the sustainability of the program.
5. With full participation of the citizens of the country or of a specific community, clear strategies and well-structured programs should be designed, with precise goals and targets to be reached at specified times. This includes the development of a functional nutritional anemia and iron deficiency surveillance system, integrated with the national health, food, and nutrition surveillance system.
6. Action-oriented research should be carried out by local institutions and will receive the necessary support.

Long-Term

1. The development of food-based approaches should be promoted to ensure adequate intake of bioavailable iron by the population.
2. All conditions that result in chronic blood loss should be reduced; if possible, they will be eliminated.

3. The necessary mechanisms, based on periodic evaluations of the situation, should be established to ensure the flexibility of existing programs and the sustainability of actions that ensure the adequacy of iron nutrition of all the population.

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APPENDIX

Five Studies in Developing Countries Addressing the Effectiveness of Iron Fortification

The Thai Study

Garby and Areekul (1974) evaluated fish sauce fortified with NaFeEDTA to a concentration of 0.5 to 1 mg of iron/ml. The average per capita consumption was estimated at between 10 and 15 ml/day. The study involved stability and blind acceptability trials of fortified fish sauce added to three typical dishes. There was no statistical preference for fortified or unfortified fish sauce in any of the three dishes. Based on bioavailability studies, the fortified fish sauce in each meal would provide close to 0.4 mg of absorbable iron.

The field study, which involved 880 persons at the start, was conducted for 1 year in two villages. One village received the fortified product and the other did not. Hookworm infection was highly prevalent and was not treated. The children, men, and women in the village consuming the fortified fish sauce increased their hematocrit by an average of about 1.5 percent above the changes observed in the control village; the differences in response were greater among the subjects with initially low hematocrits, as expected. It was concluded that the fortified fish sauce was effective in correcting iron deficiency and anemia and that the hematocrit changes would probably be greater with a longer follow-up. Consuming fortified fish sauce would cost between 0.1 and 0.3 percent of monthly salary because of a 20 to 30 percent increase in the cost of the fish sauce. Unfortunately, fish sauce is not used throughout all of Thailand.

The India Study

The Working Group on Fortification of Salt with Iron (1982) undertook a large study that followed a small pilot study in schoolchildren that proved satisfactory in stability of the product, tolerance, and efficacy in increasing Hb levels (Nadiger et al., 1980). Iron added to salt by various formulations had been proven bioavailable (Narasinga-Rao and Vijayasarathy, 1975, 1978).

This study evaluated the effect of iron-fortified salt on Hb levels in three lower-middle-income or low-income groups in rural areas (near Calcutta, Hyderabad, and New Delhi) and in an urban area (Madras City). The experimental groups, which totaled over 7,000 persons, were compared to a similar number of subjects in control groups, who consumed ordinary salt. The study lasted up to 2 years. Fortified salt was sold in village shops in one rural site and freely distributed to the households of the other three sites. Minimal medical attention was provided to all the sites, and all persons with Hb levels < 60 g/l were treated and excluded from analysis.

Anemia prevalences in young children in the rural areas ranged from 98 to 53 percent, and 23 to 9 percent in older children. In Calcutta, all age and gender groups were affected (including adult men), with anemia prevalences above 90 percent. In Madras, anemia prevalence in women was around 30 percent and in men was around 30 and < 7 percent. Prevalences among adults in the other rural areas ranged from 77 to 32 percent. In summary, rural experimental communities exhibited progressive increments in Hb, reaching an average of near 30 g/l after one year in Calcutta and near 10 g/l in Hyderabad (the rise was inversely proportional to the initial Hb deficit, as expected). In the urban center, close to a 5 g/l increment was observed at the 6-month evaluation; essentially no further increment was observed at the 12-month evaluation. The control groups showed only marginal changes. Deworming improved the response to fortified salt by about 4 g/l, from about 10 to about 14 g/l at the 6-month evaluation.

The stability of iodine in iron-fortified salt has been a point of continuous debate, and it has led to new, ongoing research with microencapsulation of the iodine with dextrin, sodium chloride, or sodium hexametaphosphate.

The cost estimate of producing and packaging the fortified salt is about US $0.01 per kilo of salt and would raise the price from 5 cents to 6 cents/kg. This means that the annual cost per capita would be between US$0.036 and US $0.072.

The production of iron-fortified salt on a commercial scale was approved by the government of India, and two private companies, in Hyderabad and Madras, are producing it. In Tamil Nadu and Rajasthan, the government has installed two large, commercial-scale fortification plants. Consideration of the impact on iron nutrition in these populations is in progress (India, National Institute of Nutrition, 1992).

The South Africa Study

Ballot et al. (1989a) studied, in a double-blind fashion, the effect of curry powder (masala) fortified with NaFe(III)EDTA at a concentration of 1.4 mg of iron/g (total mean daily intake 7.7 mg of iron). Iron nutritional status was evaluated in children > 10 years old and adult male and female members of 135 families in a South African community. A similar number of members of other families that used unfortified masala served as controls. Subjects with Hb levels

< 90 g/l were treated and excluded from the study. A total of 608 persons (335 women and 273 men) completed the study, which lasted two years. Iron nutrition was evaluated by determinations of Hb, transferrin saturation and serum ferritin, and iron stores, which were calculated with a modified algorithm based on Cook et al. (1986). The impact of fortification was determined by the change in these variables at 1 and 2 years after initiation of the program, compared with the changes observed in the unfortified subjects.

The populations studied were previously characterized by iron nutritional status, masala consumption, organoleptic characteristics, and acceptability of the fortified product (Ballot et al., 1989b), and iron absorption from the added NaFeEDTA (Lamparelli et al., 1987).

Significant and progressive improvements were seen in Hb, ferritin, and body iron stores (Figure 3-1). In men, the increments in body iron stores failed to reach statistical significance. The greatest change in all variables studied occurred in the first year, and the change was larger among those with initially low values. Transferrin saturation did not change. Estimates of total iron absorption, based on changes in iron stores, fell within the range expected from previous iron absorption studies.

The Guatemala Study

This was a 32-month-long, double-blind field study involving one highland control community (C) that received only vitamin A-fortified sugar containing 15 mg retinol as retinyl palmitate/kg as part of the ongoing national program of vitamin A fortification, and three communities that received sugar fortified with vitamin A and NaFeEDTA (130 mg of iron [1 g NaFeEDTA)/kg sugar]) (Viteri et al., 1983, 1995b). Two of the three communities (T_1 and T_2) were located in the lowlands, and one (No. 16), paired with the control community, was located in the highlands. Each community had between 1,200 and 1,700 inhabitants. Hookworm was endemic in the lowland communities; its prevalence and degree of infestation were particularly severe in community T_2, which presented severe iron deficiency.

Basic medical and antenatal care were provided in health posts that supplemented all pregnant women and treated all anemic individuals (hematocrit below 28 and 30 percent in the lowlands and the highlands, respectively). These subjects were excluded from the final analysis of the data. No treatment for hookworm was given. Analysis of the impact of iron fortification on iron nutrition was measured in a subsample through determinations of Hb, transferrin saturation, free erythrocyte protoporphyrins, and serum ferritin. Iron stores were estimated by means of the algorithm proposed by Cook et al. (1986), adapted for the Guatemalan populations and to include children above 1 year of age. Impact was measured by changes from baseline values in all of the above parameters, performed at 8, 20, and 32 months after the start of the intervention. Zinc and copper nutritional status were evaluated through plasma and urinary levels at baseline and at the 32-month evaluation. Iron urinary levels were also measured.

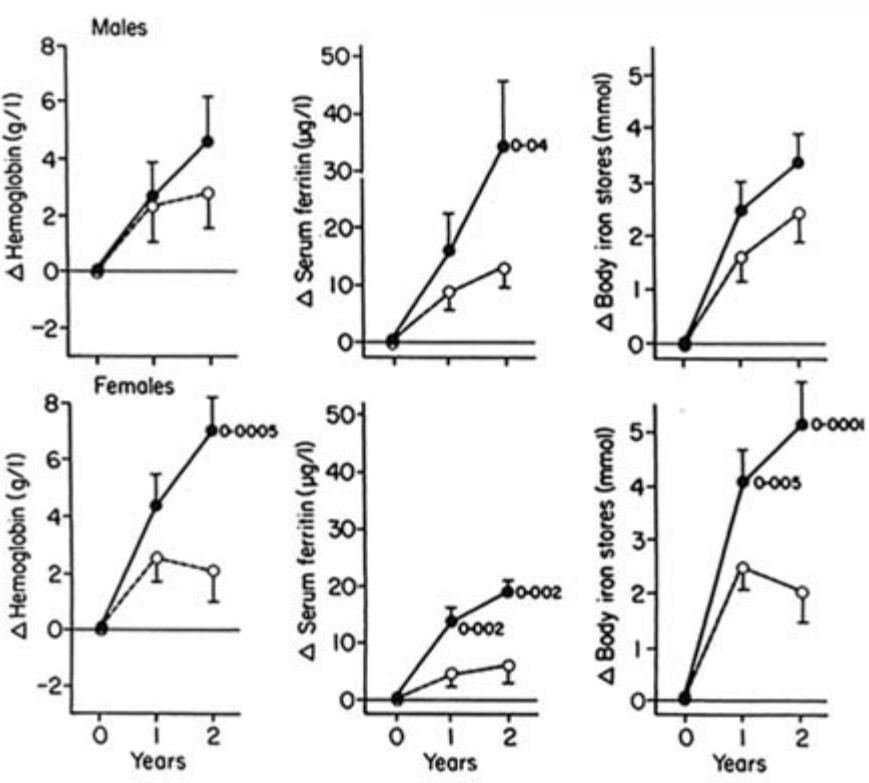

FIGURE 3-1 Changes ( ) in estimates of iron status after 1 and 2 years of iron fortification in fortified (•) and control (•) groups of males and females in South Africa (mean and standard deviation from the mean). Probabilities that the fortified populations were different from the the controls are also shown. SOURCE: Ballot et al. (1989b); reproduced with permission.

The field trial was based on previous, extensive hematological and dietary characterization of the Guatemalan population, including per capita sugar consumption and its variation by age and gender groups, locations, and other population characteristics (INCAP/ICCND, 1972; Viteri, 1973). Previous research had also measured the response to iron and iron plus folate supplementation of similar populations, indicating that anemia was almost exclusively the product of iron deficiency. Clinical trials of small-scale fortification had also been conducted satisfactorily, and the absorption of NaFeEDTA-iron and nonheme iron in Guatemalan diets had been measured previously (Viteri et al., 1978). Experimental studies had also been performed on the stability, acceptability, organoleptic characteristics, and availability of iron and vitamin A in the doubly fortified sugar and on the effect of NaFeEDTA on zinc absorption and turnover in rats. Sugar was sold in the village stores at the usual prices. Sugar consumption

was measured by family purchase records and periodic dietary evaluations. Adherence to the consumption of iron-fortified sugar was further corroborated by detection of iron in household sugar.

The results on the impact of sugar fortification on iron nutrition are best summarized by the evolution of iron stores in various age and gender groups in the communities (Figures 3-2 and 3-3). In these figures, negative iron stores reflect the severity of the iron deficit and iron reserves are expressed as values above 0, both in absolute terms and as a percentage of norms for body iron. With few exceptions, iron stores did not change significantly in the control community, but increased progressively in all age and gender groups in the fortified communities. Estimates of total iron absorption based on changes in iron stores fall within those expected from previous iron absorption studies.

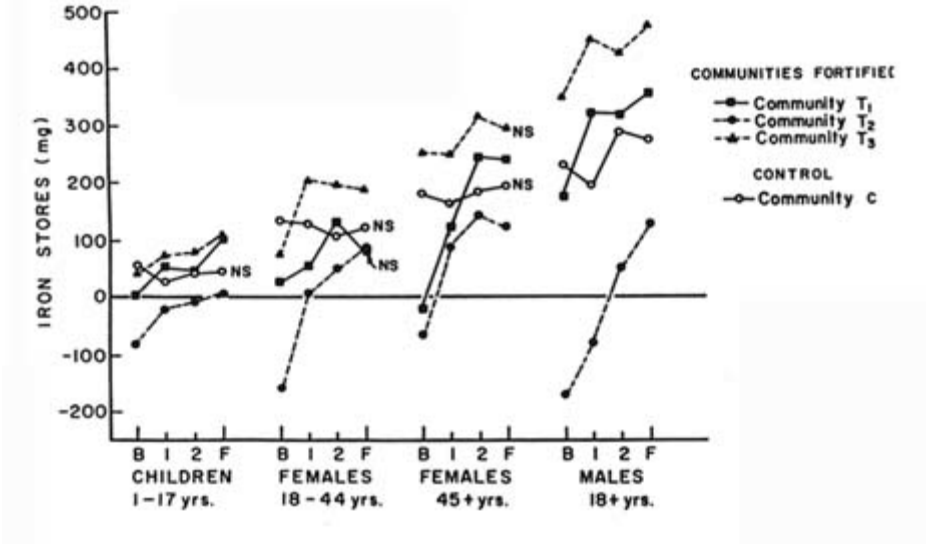

FIGURE 3-2 Mean iron stores in the four hematological and biochemical evaluation points in communities that consumed sugar fortified with NaFeEDTA (Communities T_1, T_2, and T_3) and a control community consuming regular sugar (Community C) for 32 months in Guatemala. Negative iron reserves reflect iron deficits. Communities T_1 and T_2 were in the tropical lowlands, in which hookworm is endemic. SOURCE: Viteri et al. (1995b); reproduced with permission.

Of special significance is that the members of the community most severely infected with hookworm (T_2) and the most iron deficient at the start of the study significantly increased their iron reserves with iron fortification in spite of nontreatment for parasites. Increments in iron stores decreased progressively with time of fortification, tending to reach an acceptable plateau. This indicates

that downward regulation of iron absorption was taking place. There were no individuals with biochemical indicators of iron overload.

Mean plasma zinc levels increased significantly in all communities, including the control community. Mean urinary zinc, expressed as mg/l or as mg/g creatinine, increased in all communities and reached statistical significance in communities 14 and 16. Between 16 and 20 percent of subjects in the fortified communities presented plasma zinc levels compatible with zinc deficiency at the start, and none at the end, of the study. In the control community, 16 percent persisted with plasma zinc levels compatible with zinc deficiency at the end of the study. Plasma and urinary copper levels were erratic and highly variable.

In summary, there is no evidence that zinc or copper nutritional status were compromised in any of the fortified communities. Moreover, it appears that zinc nutrition actually improved in most of the fortified communities in spite of increased urinary losses. These findings would agree with experimental evidence (Hurrell et al., 1994; Oberleas et al., 1966) and with human clinical (Davidsson et al., 1994a) and field studies (Ballot et al., 1989a,b).

Urinary iron also increased in all communities, but the increase was not significant in the control community. The highest increment occurred in community T_2, the most iron-deficient community; the population absorbed more iron, on the basis of increments in iron stores.

Annual cost estimates for sugar fortification with 1g NaFeEDTA/kilo are US$0.08 per capita (Levin et al., 1993; Viteri, 1992).

The Venezuelan Study

For many years, Venezuelan scientists, frequently under the leadership of Dr. M. Layrisse, have been studying the many aspects of nutritional anemias and iron deficiency and seeking their solution. The latest paper (Layrisse et al., 1996) is the continuation of a series of studies leading to the selection of precooked maize flour as a vehicle for iron fortification and to the use of ferrous gluconate as an iron source (Martinez-Torres et al., 1991).

The study consisted of an evaluation of the changes in the prevalence of anemia, iron deficiency, and serum ferritin levels that have taken place in cross-sectional samples of schoolchildren of low socioeconomic status at the ages of 7, 11, and 15 years between the years 1989 and 1990, and in 1992. In 1994, additional data were obtained from a sample of children in the capital city of Caracas, about 1 year after fortification of both precooked maize flour and white wheat flour was introduced in the country. The 1989–1990 and 1992 sample consisted of at least 100 children of each gender in each age bracket, representing 80 percent of the regions in Venezuela. The 1994 sample was randomly chosen from 392 public schools in Caracas.

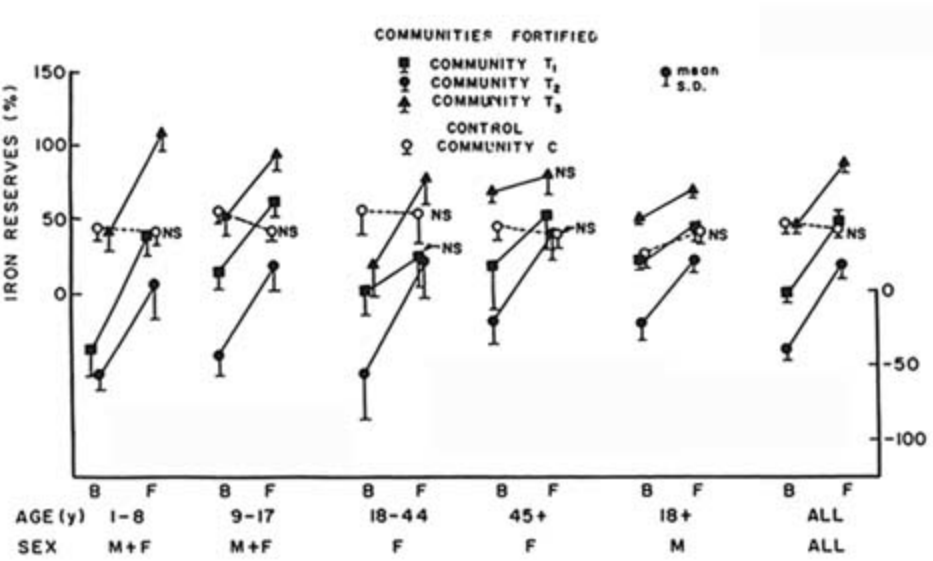

FIGURE 3-3 Iron reserves and iron deficit as "percent of norm" in the basal and final evaluations in communities that consumed sugar fortified with NaFeEDTA (Communities T_1, T_2, and T_3) and a control community consuming regular sugar (Community C) for 32 months in Guatemala. Negative iron reserves reflect iron deficits. Communities T_1 and T_2 were in the tropical lowlands, in which hookworm is endemic. SOURCE: Viteri et al. (1995b); reproduced with permission.

This study was prompted by two considerations. First, there had been a clear deterioration in the economic situation of the country from 1983 onward. This situation resulted in a decline in the quality and quantity of food available to those in the lower socioeconomic strata, which resulted in an increase in the prevalence of iron deficiency and anemia in the country. In 1989–1990, the prevalences of iron deficiency and anemia were 13.5 percent and 5.6 percent, respectively. By 1992, these prevalences had increased to 30.5 and 13.2 percent. The second consideration was the establishment of the national program for fortification of precooked maize flour with iron plus vitamins (A, B1, B2, and niacin), which was started in February of 1993 and was followed in August of the same year by fortification of wheat flour. The iron fortificant was ferrous fumarate and provided 50 mg of elemental iron /kg of precooked maize flour and 20 mg/kg of white wheat flour. Mean estimates of per capita consumption of precooked maize and wheat flour were 80 g/d and 74 g/d.

The 1994 evaluation of the Caracas public school population, compared with those performed in 1989–1990 and 1992, should reflect the effect of the iron fortification program in the schoolchildren of the city's lower socioeconomic strata. As in the national sample, iron deficiency in the Caracas children

showed an increase in prevalence from 14.1 to 36.6 percent between the years 1989–1990 and 1992, only to drop again to 15.8 percent in the 1994 survey. Low serum ferritin levels did not show a significant rise in prevalence between the years 1989–1990 and 1992, nor a fall in 1994. Anemia prevalence did show changes with time: it rose from 3.6 percent to 19.0 percent, and then fell to 9.3 percent. The interpretation of these findings is that iron fortification of precooked maize flour and white wheat flour is effectively reducing iron deficiency within 12 to 18 months of the establishment of the national programs.

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4

Prevention of Vitamin A Deficiency

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MAJOR HEALTH CONSEQUENCES

Xerophthalmia and Nutritional Blindness

Vitamin A deficiency (VAD) affects ocular tissue in two ways: by slowing the regeneration of the visual pigments following exposure to bright light and by disrupting epithelial integrity. The inability to see well in dim illumination (night blindness) is a symptom recorded in ancient Egyptian, Greek, and Assyrian medical literature and, more recently, in the writings of European physicians. Epithelial defects in ocular tissue leading to blindness were described in dogs by Magendie and in humans by Budd in the early 1800s. They observed progressive deterioration from conjunctival xerosis to corneal xerosis, ulceration, and liquefaction (keratomalacia) as a consequence of restricted diets, devoid of what we now recognize as sources of vitamin A (Wolf, 1996). Manifestations of these distinct debilitating effects were thus recognized before McCollum's discovery of an essential nutrient, coined fat-soluble vitamin A, in the early 1900s (McCollum and Davies, 1913); description of tissue changes following deprivation of this nutrient (Wolbach and Howe, 1925); elucidation of its molecular role in vision (Wald, 1968); and the recent description of its role in the regulation of genetic expression (Kastner et al., 1994; Mangelsdorf et al., 1994).

The link in humans between clinically evident symptoms and signs and a faulty diet was suggested in about 1860 and subsequently confirmed in many societies (Guggenheim, 1981; Wolf, 1996). Cure was associated with certain foods—in early times with topical application or ingestion of animal and fish liver, and in later years with ingestion of plant foods containing green and yellow pigments (Wolf, 1996). McCollum and Davies (1913), followed shortly thereafter by Osborne and Mendel (1913), described the keratomalacia-preventing, growth-limiting, fat-soluble substances isolated from efficacious foods. These substances were later designated vitamin A and carotenoids.

Steenbock (1919) postulated, and later confirmed, that carotenoid from yellow maize could support growth and prevent ocular lesions by physiological conversion to biologically active vitamin A. Since Isler et al. (1947) discovered a cost-effective way to synthesize vitamin A, cure and prevention are also possible through commercially produced, synthetic vitamin A.

Childhood Morbidity and Mortality

Working at the University of Wisconsin, and later at Johns Hopkins University, McCollum pioneered the use of mice and rats in nutrition experiments. His studies of vitamin A deprived rat colonies—and those of others—were often hampered by early deaths from respiratory and diarrheal illnesses before ocular lesions occurred. These early deaths were partly attributable to loss of epithelial integrity in tissues throughout the bodies of VAD animals, and humans as well (Chytil, 1992; Hayes, 1971; Wolbach, 1937). Similar vitamin-A-deficiency-related morbidity and mortality in human populations were not clearly demonstrated, however, until the seminal community-based studies in the 1980s of Sommer and colleagues in Indonesia (summarized in Sommer and West, 1996). These studies clearly linked increased mortality risk in preschool-age children to vitamin A deficiency, a finding later confirmed among child populations in other countries in Asia and Africa where clinical eye signs occur (Beaton et al., 1993).

Where eye signs are not evident, biochemical deficiency—that is, subclinical deficiency—is also believed to contribute to mortality risk. In free-living populations, however, an unequivocal tie to the *incidence* of infectious morbidity has not been established. *Severity* once infection is acquired provides the probable link to mortality (Ghana VAST Study Team, 1993; Underwood and Arthur, 1996). This finding implies a role for vitamin A in immunocompetence, a role suggested by an extensive review of interactions of nutrition and infection published in 1968 (Scrimshaw et al., 1968). That review concluded that VAD showed synergism with almost every known infectious disease. Recent basic studies have been unraveling the complex molecular mechanisms by which vitamin A influences the immune system and alters cellular integrity (Ross and Stephensen, 1996). The combined effect on cellular integrity and immunocompetence is believed to contribute to an annual loss of approximately 1.12 to about 3 million lives of children under 5 years of age that otherwise could be salvaged by normalizing vitamin A status (Gillespie and Mason, 1994; Humphrey et al., 1992).

Other Health Consequences

Severe vitamin A deficiency in animal models is clearly linked to other adverse health effects. These include teratogenic-developmental consequences

(Armstrong et al., 1994), adverse reproductive performance (Takahashi et al., 1975), impaired growth (Anzano et al., 1979), and depressed iron utilization (Roodenburg et al., 1996). Except for an association with anemia (Suharno et al., 1992), similar consequences among free-living human populations are less clearly attributable to vitamin A status alone. This is because in community settings, confounding is likely from coexisting nutritional deficits and disease. Nonetheless, vitamin A deficiency is undoubtedly a contributor to adverse health effects similar to those confirmed in laboratory animals, although in human populations this vitamin may not be the most immediate causative nutrient.

MAGNITUDE AND EPIDEMIOLOGY OF THE PROBLEM

Defining Vitamin A Status

Conceptually, vitamin A status can be visualized as a continuum (see Figure 4-1) from the absent or minimal tissue stores associated with symptoms and signs of deficiency to the excess tissue deposits associated with toxic symptoms and signs (Bauernfeind, 1980; Olson, 1994). Between the extremes is a relatively large zone where status cannot be easily quantified by currently available techniques (Underwood and Olson, 1993).

In practice, the limited fetal stores provided from maternal circulation launches newborns, especially those with low birthweights (Chytil, 1992), into extrauterine life at the low end of the continuum of vitamin A status. That position may be rapidly augmented postnatally in infants fed vitamin A-rich colostrum and early breast milk (Chappell et al., 1985) or supplements (Humphrey et al., 1996). From birth onward, an infant's vitamin A status on the continuum may advance by small increments, be maintained, or deteriorate, depending on the balance between dietary intake relative to growth and development needs and to disease patterns that effect vitamin A economy. Breast-fed infants do not usually show clinical deficiency for at least 4 to 6 months after birth. They may be at a marginally adequate point on the continuum, however, if breast-fed by a malnourished, vitamin A-depleted mother (Underwood, 1994a). At the same time, if breast-fed, even from a malnourished mother whose breast milk vitamin A has been improved through direct maternal supplementation (200,000 IU of vitamin A given within 2 months postpartum [WHO/UNICEF/IVACG, in press]), adequate infant vitamin A status may be prolonged beyond 6 months (Stoltzfus et al., 1993).

Vitamin A requirements (see Figure 4-2), therefore, are greatest during periods of rapid growth—infancy and early childhood, adolescence, and pregnancy—and when the vitamin is lost from the body through normal physiologic processes, such as lactation, or through nonphysiological losses brought about by frequent disease, such as malabsorption, diarrhea, and febrile infections (FAO/WHO, 1988).

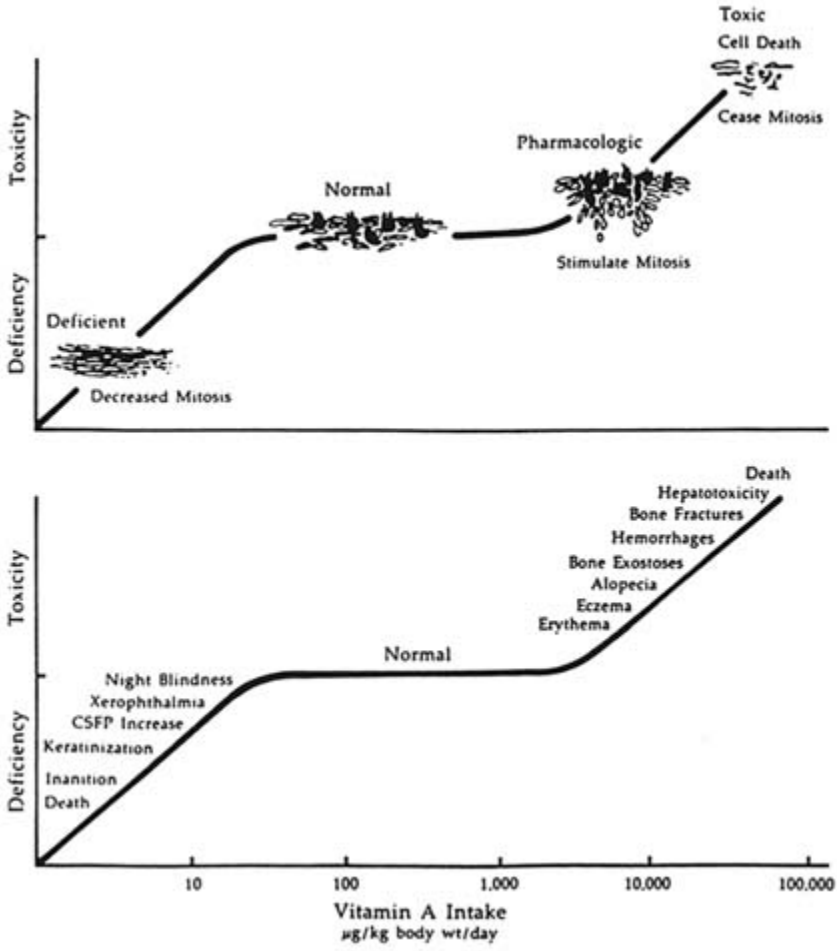

FIGURE 4-1 The logarithmic plot of vitamin A intake is depicted as a function of the biological response of man and animals in terms of deficiency, normalcy, and toxicity. The scheme at the top illustrates the response of a typical mucous epithelium, but is probably applicable to other undifferentiated blast-cell populations as well. The bottom curve indicates the clinical manifestations resulting from the altered cell function in deficiency and toxicity of vitamin A. SOURCE: Bauernfeind (1980), reproduced with permission.

Recognition of factors that influence vitamin A balance provides a foundation for understanding the epidemiology of VAD (Oomen et al., 1964; Tielsch and Sommer, 1994; Underwood, 1993).

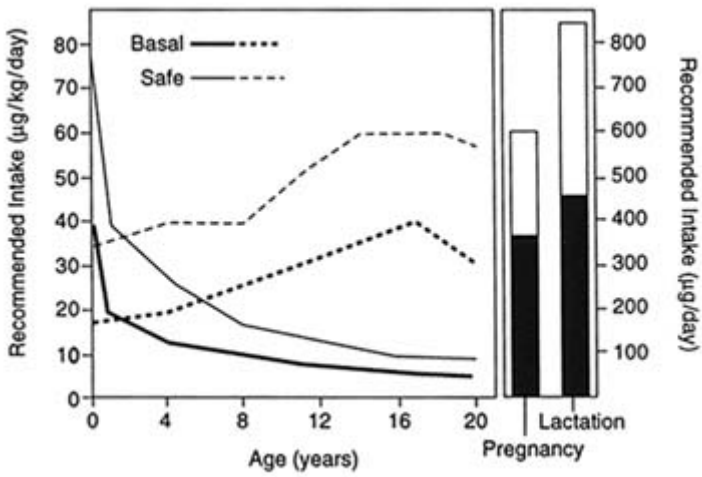

FIGURE 4-2 Recommended intake of vitamin A. SOURCE: Adapted from FAO/WHO (1988).

Extent of the Problem

Since the debilitating—and sometimes fatal—link of VAD to health is well-established, and effective and relatively inexpensive food sources and synthetic vitamin A are available for VAD prevention and control, why does a global public health problem persist? Clearly the fault lies in the application of insufficient or ineffective knowledge to the implementation of programs to rectify uneven resource distribution among and within affected populations. WHO estimated in 1995 that at least 3 million children exhibit xerophthalmia annually—they are clinically deficient and at risk of blindness. An additional 250 million children under 5 years of age are at risk of deficient vitamin A status (based on the prevalence of serum retinol distributions below 0.70 µmol/L); they are subclinically deficient, and at risk of severe morbidities and premature death (WHO, 1995a). These estimates do not include pregnant and lactating women who are in areas of endemic childhood VAD, and are thus likely to be in poor status, but for whom epidemiological data are quite limited. A high prevalence of maternal night blindness (Katz et al., 1995) and low breast milk levels of vitamin A (Newman, 1993) are reported in such areas. A lack of sensitive, survey-applicable, nonclinical indicators specific to VAD, however, has hampered population-based evaluation of status among reproductive-age women and other age and gender groups (WHO, 1996a).

Risk Factors

Age

Clinical and subclinical VAD are most prevalent in children 6 months through 5 years of age. This period is characterized by high requirements to support early rapid growth, the transition from breast-feeding to dependence on other dietary sources of the vitamin, and increased frequency of respiratory and gastrointestinal infections. Although growth rates decline sharply during infancy, decreasing the requirement for vitamin A per kilogram of body weight, the absolute quantity of the vitamin needed daily increases with growing total body mass (see Figure 4-2, based on FAO/WHO, 1988). If average dietary vitamin A intake from food progressively increases with body mass, body stores are likely to increase by small increments with advancing age. If diet is inadequate, and no vitamin A supplement is given, body reserves may only be maintained, or will decline if frequent disease, so prevalent among toddlers, tips the balance downward. How quickly the deficit can be restored depends on its magnitude and the repletion-rehabilitation program followed (see Figure 4-3).

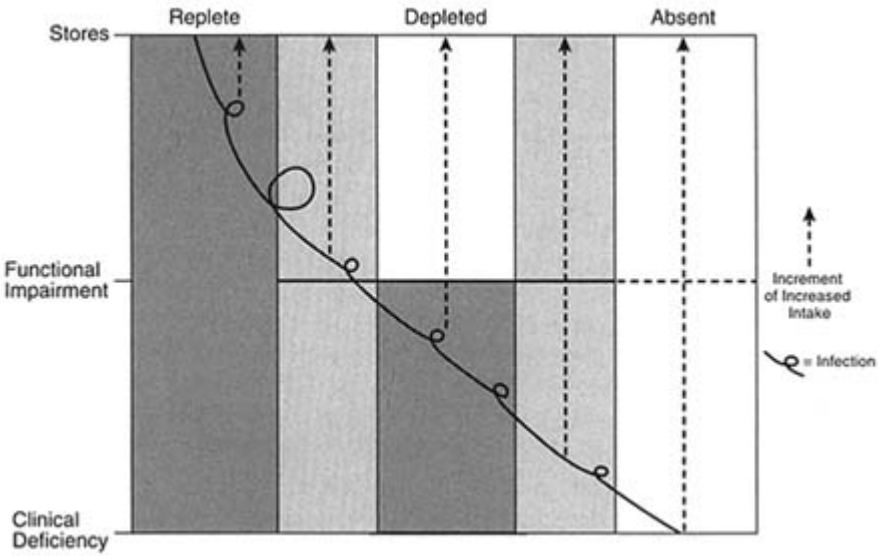

FIGURE 4-3 Vitamin A status.

Gender

There is no consistent, clear indication in humans of a gender differential in the requirement for vitamin A during childhood. Growth rates—and presumably need for vitamin A—from birth to 10 years for boys are consistently higher than those for girls (WHO, 1995b). In the context of varied cultural and community settings, however, variations in gender-specific practices for the feeding and care of children are likely to subsume a small gender differential in the requirement to account for reported gender differentials in xerophthalmia prevalence. Pregnant and lactating women, of course, require additional vitamin A to support maternal and fetal tissue growth and lactation losses that are not endured by other postadolescent adults (NAS, FNB, IOM, 1990).

Quality of Diet

Dietary sources of biologically active vitamin A are found preformed in some animal foods or as provitamin carotenoids from plants. There is no specific human requirement for carotenoids apart from their potential conversion to biologically active retinoid. Preformed vitamin A is highly bioavailable, whereas the bioavailability of provitamin A carotenoids varies with the kind of plant source (Rodriguez-Amaya, 1997). The bioavailability of the provitamin A carotenoids from plants is greatly influenced by the nature of the embedding matrix (i.e., fibrous, dark green leafy vegetables [DGLV] or soft-fleshed yellow/orange vegetables and fruits) and the composition of the accompanying meal. Carotenoids, once released in the gastrointestinal tract from the embedding matrix, are only absorbed when fat is concurrently available. Dietary fat is needed to stimulate intestinal and pancreatic secretions. These secretions contain lipolytic enzymes for fat digestion, and phospholipids and bile salts needed for micelles to form and solubilize both preformed vitamin A (Blumhoff et al., 1991) and carotenoids (Erdman, 1988). Only micelle-solubilized carotenoids gain entrance to enterocytes where bioconversion to retinol, or intact transfer to chylomicra, occurs; that is, they become bioavailable.

Disease Occurrence

Infectious diseases contribute to vitamin A depletion. Enteric infections may alter absorptive-surface area, compete for absorption-binding sites, and increase urinary loss (Alvarez et al., 1995; Solomons and Keusch, 1981). Febrile systemic infections also increase urinary loss (Stephensen et al., 1994) and metabolic utilization rates. Disease is often associated with precipitating ocular signs in the presence of latent deficiency (Curtale et al., 1995; Feacham, 1987). Infection with the measles virus is especially devastating to vitamin A metabolism,

adversely interfering with both efficiencies of utilization and conservation (Hussey and Klein, 1990; Sommer and West, 1996). Severe protein-energy malnutrition (PEM) affects many aspects of vitamin A metabolism, and even when reserve retinyl-ester stores are adequate, it can prevent transport-protein synthesis, resulting in immobilization of existing vitamin A stores (Arroyave et al., 1967; Smith et al., 1973; Smith et al., 1975).

Seasonality

In endemic VAD areas, fluctuations in the incidence of VAD throughout the year reflect the balance between intake and need. Times of food shortage (particularly of vitamin A-rich foods), periods of peak incidence of common childhood infectious diseases (diarrheal, respiratory, and measles infections), and periodic seasonal growth spurts affect the balance.

Seasonal food availability can influence VAD prevalence in two ways. First, it directly influences access to provitamin A sources. Scarcity prevails in the hot, arid months and gluts are seen during harvest seasons—in the case of mangoes, for example (Marsh et al., 1995). Second, seasonal growth spurts in children frequently follow postharvest increases in energy and macronutrient intakes, usually from staple grains (such as rice) and tubers (light-colored yams, for example) that are not good sources of some of the micronutrients, including vitamin A, that are needed to support the growth spurt (Sinha and Bang, 1973).

Cultural Factors

Food habits and taboos often restrict consumption of potentially good food sources of vitamin A, such as mangoes and green leafy vegetables. Culture-specific practices in the feeding of children, adolescents, and pregnant and lactating women are common (Chen, 1972; Johns et al., 1992; Mele et al., 1991). Illness-related and pre- and postparturition proscription in the use of "cold/hot" (yin/yang) foods pervade many traditional cultures (Mahadevan, 1961). Such influences alter shortand long-term food distribution within families that may only be detected by dietary intake surveys disaggregated by age and gender and/or in-depth focus group discussions (Kuhnlein and Pelto, 1997). Culture-specific information of this kind is pivotal to the design of food-based behavior change interventions.

Clustering

Epidemiological studies repeatedly report clustering of VAD, presumably because of the concurrent occurrence of several risk factors. This clustering may occur at several levels, from the national arena to neighborhoods and households

(Katz et al., 1993). Identifying the level at which clustering occurs is an important consideration in the selection, design, and targeting of VAD-control strategies.

ECONOMIC COSTS OF VAD

The cost of VAD to society includes the burden of the prolonged management and care needed for such common childhood diseases as diarrhea and measles, and when deficiency is severe, provision for lifelong care of blinded victims. To illustrate the true global societal cost, Foster and Gilbert (1996) compared the cumulative disabled years in developing countries from childhood blindness with the total from unoperated cataract, the major cause of blindness after 50-60 years of age. The estimated 1.5 million blind children have a life expectancy of 50 years, equivalent to approximately 75 million years of disability. About 16 million older adults, with a much shorter life expectancy of 5 years, account for 80 million blind years. The years of economic burden to society from these two preventable causes of blindness are thus comparable, even though there is a tenfold difference in the number of individuals affected. Moreover, these costs do not account for the premature loss of life among the VAD-blinded, as well as among the subclinically VAD-deficient child population under 5 years of age. The real tragedy is that vitamin A-related childhood blindness—accounting for at least half of the total number of blinded children—can be treated or prevented (WHO, 1992), and subclinical VAD-related deaths can be substantially reduced (Beaton et al., 1993). VAD, therefore, is costly to the individual child in lost opportunity, and it has economic and social costs for the family, community, and nation as a whole.

INDICATORS OF VAD

Identification of Groups and Populations

A standardized classification system for xerophthalmia (clinically evident VAD) and universally accepted criteria for defining a public health problem were agreed upon in 1982 (WHO et al., 1982). These criteria (see Table 4-1) remain appropriate for identifying populations at high risk of vitamin A-related, blinding malnutrition—populations to the far left of the vitamin A status continuum (Figure 4-1). They are inadequate, however, for identifying populations with *subclinical* deficiency—tissue concentrations of vitamin A low enough to have adverse health consequences, even in the absence of xerophthalmia, WHO's current definition of VAD (WHO, 1996a).

TABLE 4-1 Biological Indicators of Clinical Vitamin A Deficiency: Xerophthalmiaa in Children 6–71 Months of Age

Indicator	Minimum Prevalence (%)
Night blindness in children 24–71 months of age (XN)	> 1.0
Conjunctival xerosis/with Bitot's spot (X1B)	> 0.5
Corneal xerosis/ulceration/keratomalacia (X2, X3A, X3B)	> 0.01
Corneal scars[b] (XS)	> 0.05

NOTE: Prevalence of any one or more of the indicators indicates a public health problem.

[a] In addition, a serum level of vitamin A (retinol) has been used with the clinical classification to provide supportive evidence of an important problem. A prevalence of > 5 percent of serum levels < 0.35 µmol/l is strong corroborative evidence of any clinical criteria met to identify an urgent public health problem.

[b] Lack of a history of traumatic eye injury or use of topical traditional medicines increases the specificity of this VAD indicator.

Unfortunately, there is no practical, single indicator of adequate specificity and sensitivity to detect subclinical deficiency under community conditions—that is, populations in the intermediate left portion of the vitamin A-status continuum (see Figure 4-1). For this reason, WHO recommends that two or more indicators be used, at least one of which is biological and below the agreed upon cutoff points provided in Table 4-2.

Where it is not possible to obtain two biological indicators, WHO suggests that one such indicator should be supported by a composite of at least four of the indirect demographic and ecological risk factors given in Tables 4-3A and 4-3B. Two of the four indirect indicators should be related to nutrition and diet (Table 4-3A). Socioeconomic indicators (Table 4-3C) are also useful qualitative indicators of the characteristics of high-risk populations. The cutoff values suggested in Table 4-3 resulted from the reflections of a WHO-sponsored consultation of experts. The group pointed out the need for additional confirmation of the utility of the values and suggested prevalence cutoffs. These ecological indicators reflect a context of dietary inadequacy and social and economic deprivation that have been associated with endemic VAD through epidemiological investigations (Sommer and West, 1996). Their usefulness is in identifying high-risk areas and populations, *not* individuals. Biological indicators are needed to confirm that a significant public health problem exists.

Monitoring Intervention Impact and Outcome

Appropriate indicators in the monitoring of intervention impact will vary in accordance with the intervention objective. For example, program objectives

may be to improve coverage of recipients of vitamin A supplements; to ensure that a vitamin A-fortified food meets quality-assurance standards or is selected for consumption by target groups; to cause a change in food-consumption behavior, such as the frequency of consumption of DGLV; or to increase the year-round availability of vitamin A-rich food in household or community gardens. The appropriate intervention-specific *impact* indicator(s) for each of these objectives will differ; in some cases process indicators will be used, in others, biological indicators are appropriate (Table 4-3). If the desired *outcome* of the intervention is to document a change in the vitamin A status of the recipient population, the biological indicators in Tables 4-1 and 4-2 are appropriate.

Resource availability can limit the feasibility of direct biological evaluations because these indicators are usually more costly to obtain and evaluate than indirect indicator data. In such situations, outcomes derived from metabolic and/or controlled community studies lend credence to causative inferences from similar outcomes of interventions implemented in less rigorously controlled community studies. The inability to perform biological evaluations alone should not prevent initiation of, or stop, VAD control programs when and where such programs are needed.

TABLE 4-2 Biological Indicators of Subclinical Vitamin A Deficiency in Children 6–71 Months of Age (percent)

Indicator (cut-off)	Prevalence Below Cutoffs to Define a Public Health Problem and Its Level of Importance		
	Mild	Moderate	Severe
Functional			
Night blindness (present at 24–71 months)	>0 to <1	≥1 to <5	≥5
Biochemical			
Serum retinol (£0.70 µmol/l)	>0 to <10	≥10 to <20	≥20
Breast milk retinol (£1.05 µmol/l)	<10	≥10 to <25	≥25
RDR •20%)	<20	≥20 to <30	≥30
MRDR (ratio • 0.06)	<20	≥20 to <30	≥30
+ S30DR (•20%)	<20	≥20 to <30	≥30
Histological			
CIC/ICT (abnormal)	<20	≥20 to <40	≥40

TABLE 4-3A Ecological Indicators of Areas and Populations at Risk of VAD: Nutrition and Diet-Related Indicators

Indicator	Suggested Prevalence
Breast-feeding pattern; 86 months of age; ≥6–18 months of age	>50% not receiving breast milk; <75% receiving vitamin A-containing foods in addition to breast milk, 3 times/week
Nutritional status (< -2SD from WHO/ NCHS reference)	
Stunting (<3 years of age)	≥30%
Wasting (<5 years of age)	≥8%
Low birthweight (<2,500 g)	≥15%
Food availability; Market; Household	DGLVs unavailable ≥6 months/yr <75% households consume vitamin A-rich foods 3 times/week
Dietary patterns; 6–71 months; children; Pregnant/lactating women	<75% consume vitamin A-rich foods at least 3 times/week
Semi-quantitative/qualitative food frequency	Foods of high vitamin A content eaten <3 times/week

NOTE: The suggested prevalence cutoff levels are arbitrary. The group of indicators, however, should be given greater weight in identifying high-risk populations than is given to the other ecological indicators noted below.

TABLE 4-3B Illness-Related Indicators in Children 6–71 Months of Age

Indicator	Suggested Prevalence
Immunization coverage at 12 months of age	<50% fully immunized
Measles case fatality rate	≥1%
Diarrhea disease rate (2-week point prevalence)	≥20%
Fever rates (2-week point prevalence)	≥20%
Helminthic infection rates, particularly ascaris	≥50%

NOTE: The suggested prevalence rates are arbitrary and are suggested only to assist in the relative ranking of vulnerability of populations. They are best used in association with a biological indicator and more than one of the nutrition- and diet-related indicators.

TABLE 4-3C Socioeconomic Indicators

Indicator
Levels of maternal education and literacy
Income/employment
Water supply and level of sanitation
Access to health and social services
Access to land
Access to agricultural services/inputs

CRITICAL ELEMENTS FOR SUCCESSFUL NUTRITION INTERVENTION PROGRAMS

Characteristics of successful community nutrition programs were reviewed in 1989 by the International Nutrition Planners Forum (International Nutrition Planners, 1990). Critical elements were identified within six categories: (1) political commitment; (2) community mobilization and participation; (3) human resources development, such as training, retraining, and supervision; (4) targeting; (5) monitoring, evaluation, and management information systems; and (6) replicability and sustainability. These general criteria, as well as additional factors found to be specific to the vitamin A context, were the framework used to judge the vitamin A control programs reviewed for this paper.

This paper also draws upon the 1994 report of the United Nations Subcommittee on Nutrition (SCN) of the Administrative Committee on Coordination (ACC). Impact evaluations of about 46 trials and large-scale programs to prevent VAD were summarized (Gillespie and Mason, 1994). That evaluation of some programs is updated here, and the information extended to new program evaluations. Only a few specific, successful interventions are highlighted in detail to illustrate the elements associated with success or failure in a given context. Other programs are referenced briefly, as appropriate, to corroborate elements associated with success and that transcend a specific context. No attempt is made to comprehensively review or reference all intervention programs or to provide in-depth detail. References are provided to original reports or recent reviews so readers can find the missing details they require.

APPROACHES TO THE PREVENTION OR CORRECTION OF VAD

Vitamin A intervention approaches are commonly grouped into two main control strategies: (1) *direct increase in vitamin A intake* through dietary modification with natural or fortified foods and supplements and (2) *indirect public health measures* to control disease frequency. *Information, education, and communication (IEC)*, including *social marketing* and specific vitamin A-oriented *nutrition education*, may or may not accompany each of the above interventions. Fortification is a food-based approach, but for clarity in this paper, it is considered separately from other food-based approaches. Vitamin A supplementation is also considered separately. Public health disease control measures are only briefly acknowledged because those interventions are not the primary focus of this review, except as they complement direct VAD-control strategies. Apart from controlled research projects (for example, with intervention and matched control communities), one can seldom evaluate the "success" of a single community-based intervention implemented over time. The presence

of other national and community development programs with variable coverage and impact on target populations that overlap with vitamin A-specific interventions is customary. Two examples include national economic development and community poverty alleviation schemes and increased measles immunization coverage in populations also given periodic vitamin A supplements.

Food-Based Approaches

As noted earlier, VAD as a public health problem is the result of a faulty diet that supplies inadequate bioavailable sources of vitamin A. The immediate causative factors vary among societies, but include limited availability (for economic or other access reasons); cultural taboos and/or lack of knowledge that leads to inappropriate food practices (particularly in feeding children and pregnant and lactating women); frequent illness affecting the efficiency of absorption and utilization of nutrients, as well as appetite; lack of sufficient dietary fat to facilitate absorption, especially of carotenoids; and food processing, storage, and preparation practices that cause excessive losses. To design successful food-based prevention or correction approaches, one must consider the relative importance of causal factors and the resources available—or that can be generated—to ameliorate them within the specific local context for implementation (Kuhnlein et al., 1996).

Dietary Modification: Where Food Sources of Vitamin A Are Available but Underutilized

It is ironic that VAD prevalence among preschool-age children is high in many societies where provitamin A carotenoid sources are abundant. In these circumstances, behavior modification through dietary counseling and nutrition education is clearly the logical choice. Yet the general consensus is that these approaches have been ineffective in bringing about significant, sustained, communitywide behavior changes in food consumption patterns. An extensive review of the effectiveness of strategies used to *deliver* nutrition education—not what the nutrition science content was—of 217 well-designed and carefully evaluated experiences in the United States concluded that nutrition education "works" when behavior change is the objective and the intervention is designed to achieve that goal, not just to transfer knowledge or change attitudes (Contento et al., 1996). Market research methodology used in the private sector to achieve consumer behavior modification—social behavior marketing or social mobilization—is now being applied in international settings in the public sector to achieve the socially desirable, health-linked behavioral goal of improved nutritional status (Parlato, et al., 1992; Seidel, 1996). Smitasiri (1994) suggests that earlier ineffectiveness in changing food behaviors in resource-poor communities

through nutrition education may relate to the lack of a systematic analysis of the local situation. Such analyses could have led to the design of appropriate interventions that are oriented toward community action, embedded in the prevailing culture, and incorporate the necessary supportive social, political, and organizational structures required for sustainability.

Thailand's Experience in Applying a Social Marketing Methodology to Increase the Utilization of Locally Available Vitamin A-Rich Foods*

Context

VAD among preschoolers in north and northeast Thailand is largely a subclinical problem, potentially controllable through locally available, inexpensive foods. The area is noted for its poor economic and environmental conditions. Although highly bioavailable animal sources of vitamin A are present, they are expensive, and fruit sources of provitamin A carotenoids (mango) are highly seasonal. Among locally available vegetables, ivy gourd (a variety of vitamin Arich DGLV) is common throughout the year, inexpensive, culturally acceptable, but underutilized because it is held in low esteem.

Design of the Intervention

A situational analysis, including formative research, was conducted with the active participation of local politicians; academicians in health, nutrition, and the social sciences; and the proposed recipient community (including representative mothers). After collectively considering the results of the analysis, a strategy was planned that incorporated active, multidisciplinary community involvement. The design agreed upon fit into the larger community development strategy. It promoted consumption of vitamin A-rich foods and the use of fat/oil in their preparation, and gave particular emphasis to increasing the production and consumption of ivy gourd through an intensive social marketing (mobilization) effort.

Qualitative and quantitative impact monitoring (process) and outcome (biological) evaluations were integral parts of the program design. The intervention plan was implemented only after systematic pretesting and appropriate adjustment to the local context. Iterative, cyclical monitoring throughout the implementation phase allowed the accumulating experience to serve as a guide in adjusting future actions. Promotional activities were embedded in the social activities and organizational structures of the community —school and community

* Smitasiri et al., 1992; Smitasiri, 1994.

gardens were used for production; recipes and menus appropriate for school lunch programs and family meals were developed; communitywide promotional materials and activities were planned with the active involvement of political, educational, health, and private sector leaders; and the "ivy-gourd man" (a clown clothed to represent an ivy gourd leaf) participated in local social events that attracted all ages and community groups. Regional radio and television spots and a promotional song recorded by popular Thai singers reinforced local activities and spread the message to an expanded audience. Activities related to the program were identified by a prominently displayed program logo—the ivy gourd.

Implementation and Evaluation

The intervention phase was in effect for two years before the program was evaluated. This evaluation focused on evidence of increased utilization of ivy gourd by the community, particularly among the preschoolers and mothers who had been targeted for behavior change. Measures of pre- and postintervention knowledge, attitudes, and reported food consumption behavior (KARB), in addition to 24-hour dietary recall evaluations, were obtained for both the ivy gourd and fat, particularly for women and preschool-age children. Vitamin A status was monitored through changed prevalence of ocular symptoms and low serum retinol values in children. Evaluations were done by university teams that worked independently of the project implementation team; knowledge, attitudes, and practices (KAP) evaluations were performed by the Faculty of Social Sciences and Humanities, anthropological evaluations were done by the Institute for Population and Social Research, and changes in vitamin A status were tracked by the Institute of Nutrition's Division of Community Nutrition.

Results

Statistically significant improvement in KARB occurred in the consumption of vitamin A-rich foods and the use of fat/oil in their preparation, particularly relative to ivy gourd. These changes penetrated from provincial officials through the district, subdistrict, and community levels, to reach the targeted audience of mothers and children. The dietary evaluation (and indirect indicator of vitamin A status) also showed an increased consumption of vitamin A-rich foods, including ivy gourd and fat/oil among vulnerable groups, with the exception of infants. A decreased prevalence of ocular signs of VAD (night blindness) was recorded, but no notable improvement was detected in serum retinol levels (project personnel noted that technical problems encountered in storage and delayed analysis of serum samples may have invalidated comparisons between intervention and control areas).

The following project elements were associated with success:

- A combined mass media and interpersonal education and communication approach was utilized to achieve broad and communitywide coverage, while at the same time achieving specific coverage of the targeted groups.
- Messages were prepared from a multidisciplinary perspective that accommodated local resources and culture in both message construction and dissemination.
- Image enhancement was used to broaden social acceptance and consumption of an underutilized, locally available, affordable, familiar food product.
- Behaviors were embedded in community structures—for example, schools and social activities.
- Backup problem-solving and supply-availability support was sought from local resources, including agricultural extension services, for production questions, availability of seedlings, pest control, and fertilizer.
- A sense of community ownership was created through community participation in the design and management of parts of the project.
- Participation of community political and business leaders assured a strategy that was consistent with the existing community development plan and with the larger development policy of the country (this enhanced political acceptance through the political levels, from community to national).
- Critical elements, thought to be indispensable for replicability and sustainability for the continuation of gains beyond the project's life, were built into the program (only revisiting the project area, however, will determine if successful intervention components have been replicated in other projects and desired activities and behaviors sustained).

The constraints encountered included:

- Sustained interest and participation continued as long as the program was active, but waned when the social marketing activities were less intense.
- The cost of the intensive social marketing could not be sustained by the community, although there was evidence that many of the nutrition and health concepts had been internalized and the community had continued the required behaviors beyond the project period.
- Replicability of the project as designed depends on the availability of funds to launch comparable intensive efforts in other communities or the ability to scale down the effort to a level that localities can afford.

OTHER COUNTRIES' EXPERIENCES

Social marketing projects in Indonesia, Bangladesh, and the Philippines were also evaluated as successful in increasing consumption of available vitamin A-rich foods. Unlike Thailand, each of these countries also has extensive programs for periodic distribution of encapsulated vitamin A supplements (VAC) because xerophthalmia is—or has been, in Indonesia—a public health problem. Large-scale social marketing projects were undertaken in each country to change attitudes and behaviors constraining consumption of increased quantities of vitamin A-rich food and capsule coverage (Favin and Griffiths, 1991; Pollard and Favin, 1996). Clinical examinations were done to detect changes in xerophthalmia prevalence, but biological evaluations, such as serum retinol, were not included.

Improvement in attitudes and behaviors concerning the consumption of vitamin A-rich foods was demonstrated in all sites. Social marketing programs in Bangladesh, however, were ineffective in increasing VAC coverage (Ali et al., 1993), but successful in Indonesia (Reis et al., 1996). The key components of success in increasing the consumption of vitamin A-rich foods were similar in all three sites and like those found in the Thailand project:

- The development of intervention and message strategies was based entirely on local consumer attitudes, practices, and behavior.
- Messages of product-image definition were used to target specific DGLVs and to reposition their image; that is, the value of DGLVs expanded from eye health to general health.
- Creative solutions were added to overcome defined and targeted local resistance points.
- A media mix of mass (to broaden coverage) and interpersonal (to reinforce sustained behavior change) communications was used, with some emphasis on application at point-of-sale (the markets where most women buy their DGLVs).

A major difference from the Thailand project was that community participation—embedding—was not emphasized. It was viewed as too time-consuming for the "relatively short periods of donor funding." Also, multiple DGLVs were promoted, rather than a single product. The sustainability of desired change in food behavior beyond the period of donor support has yet to be documented.

Based on the lessons learned in pilot projects, Indonesia has scaled up its social marketing strategies targeted both toward improved VAC coverage and increased consumption of vitamin A-rich foods (Shaw and Green, 1996). Internally supported national, provincial, and community mass media strategies are being implemented to broaden audience coverage. National nongovernmental

organizations (NGOs) (women's groups) complement the mass media strategies to attain the interpersonal contact through home visits that is needed to reinforce desired modifications in behavior and to contact hard-to-reach and high-risk populations (such as poor urban residents and those not attending local health posts).

Other Social Marketing Experiences

Features of seven nutrition communication programs are summarized in a recent IVACG publication (IVACG, 1992). Applications in Brazil, India, Mauritania, and Nepal are added to some of the projects noted above. Vitamin A intervention programs carried out in this contextual diversity almost universally showed that applying a social marketing methodology in the development of nutrition education messages and other communication strategies can quite rapidly (in 18–24 months) modify attitudes and food behaviors of vulnerable groups to increase their vitamin A intake from familiar, available, underutilized DGLVs. The exception in most targeted social behavior modification projects was 6- to 12-month-old infants; resistance to feeding them DGLVs persisted. When focus group discussions indicate such resistance in a given population, social marketing should consider alternative, locally available vitamin A-rich foods—such as yellow fruits and orange vegetables—for this age group.

The primary *constraint* to replicability and sustainability of social marketing strategies in most projects is *cost.* Caruaru, Brazil, was a notable exception. In Caruaru, dissemination of the communication effort was confined to biannual periods when supplement distribution took place, and the communication package was developed using affordable local resources (IVACG, 1992). Indonesia also has decentralized parts of its social marketing strategy to local agencies, increasing affordability, commitment, and autonomy. In Bangladesh, a low-cost, locally developed and implemented nutrition intervention and educational and motivational project was also effective in reducing night blindness in an 18-month period (Yusuf and Islam, 1994).

Lessons Learned in Behavior Modification Where Vitamin A-Rich Foods Are Available

- A social marketing strategy using a multimedia communication mix is essential. Mass media is necessary to achieve broad audience coverage and interpersonal contact is needed to reinforce desired behavior change in targeted audiences. At least in part, the strategy needs to be decentralized—and affordable—to the lowest effective administrative unit.

- The development and delivery of media materials should be founded on local perceptions and resource availability.
- Political, public, and private sector commitment and ownership from the national to the local level is needed for sustainability. External financial and technical assistance may facilitate start-up of intervention activities, but the programs should not depend on such aid for their continuation.
- Community-level monitoring provides intermittent process feedback and the flexibility to meet changing situations. Periodic repositioning of components within the strategy will be required to ensure forward progress toward stated objectives.

Dietary Modification: Home and Community Provisioning to Increase Availability of Vitamin A-Rich Foods

Home and community gardening has been promoted for many years to control nutritional deficiencies at the household level through increased availability of nutrient-rich foods (see UNU *Food and Nutrition Bulletin*, 1985, for examples). This approach has special appeal in meeting family vitamin A—as well as multiple micronutrient—needs. In theory, these needs can be met by locally familiar, low-cost, provitamin A-rich vegetables and fruits that can be produced on small land areas with manageable time commitments. Needed resources can be developed (for example, seed banks and nurseries) and sustained by communities with little use of outside expertise. By its nature, this intervention necessitates a high degree of household and community involvement. An adequate water supply, however, can be a major constraint to initiating horticulture activities, render them highly seasonal, or restrict them to limited geographic areas (Brownrigg, 1985).

Until recently, few gardening projects were evaluated for biological effectiveness; of those few, changes in nutritional status were rarely demonstrated. This failure to document desired biological outcomes was attributed to the preference of farmers—even women farmers—to sell what they produced and spend only a small portion of the income earned for food (Brun et al., 1989; Florentino et al., 1993; Marsh et al. 1995). Recent large-scale homestead garden projects were designed to address barriers to achieving biologically effective programs. They have incorporated a communication and social marketing strategy designed to modify behaviors in household management of garden products. The strategy is to increase production goals to allow limited sale, as well as to encourage increased consumption. The success of these revamped projects is documented by improved health and nutritional status outcomes, as well as by measurement of the more usual production, KAP, and indicators of the impact of dietary intake programs. Examples from some recent successful projects in Bangladesh, India, and Vietnam are briefly reviewed.

Experiences in Bangladesh with Promotion of Home Gardens

Context. Xerophthalmia is highly prevalent in Bangladesh, and prevalence has not decreased substantially, even with the program of the biannual distribution of high-dose supplements that has been in place since 1973. In recent years, two large gardening projects have been undertaken, one sponsored through NGOs with the overall assistance of Helen Keller International (HKI), and one project under the sponsorship of World-view International Foundation (WIF). Very significant elements of both projects are a focus on women; the use of community agricultural extension expertise to provide low-cost gardening techniques and resources; and innovative, locally adapted IEC (Ali et al., 1993; Greiner and Mitra, 1996). In addition, both projects developed information systems for systematic monitoring and evaluation. The HKI information system was developed for continuous, interactive, community-managed monitoring.

Results. Both projects demonstrated increased consumption of several kinds of vitamin A-rich vegetables and fruits produced in the home and community gardens (Bloem, 1996; Greiner and Mitra, 1996). The prevalence of night blindness was reduced from baseline values. Benefits were directly associated with the number of varieties of vitamin A-rich foods promoted. In addition, both projects demonstrated replicability by successful expansion into new communities. Focusing efforts on women had important "gender-empowering" effects, and even though women sold part of the crops produced, their households benefited through increased food security, greater income, and healthier children (Marsh et al., 1995). Long-term sustainability remains to be demonstrated, but the critical elements needed for this to occur, including NGO backup in implementation and commitment of the national government, are thought to be present (van der Haar, 1992). HKI is now focusing efforts to implement a substantially larger project that includes the expanded involvement of local NGOs in management to reduce costs and to favor community self-sufficiency (Marsh et al., 1995).

West Bengal, India: Experience with Horticultural Interventions in a Drought-Prone and Poverty-Stricken Rural Area*

Context and Design. Committees at the state, district, block, and village levels provide guidance, coordination, and implementation. They have been extensively involved in the program from the initiation of a project to introduce home gardens and nutrition education in this socially, economically, and environmentally deprived area of India (FAO, 1996). Formative research provided

* FAO, 1996.

the basis for the nutrition education components. Field implementers were selected from local areas and trained in nursery development, home gardening, and food storage and preservation. One feature of the project was the involvement of academicians from the local university, who addressed the practical nutritional aspects of home gardening, such as modification in home-cooking practices for improved nutrient preservation. A variety of DGL Vs and yellow fruits were promoted and supported through local nurseries.

Results. After 18 months, project evaluation documented improved KAP, greater consumption of DGL Vs and some fruits (papaya), and a reduction of xerophthalmia, all indicators of at least short-term success. It is too soon to determine if the favorable changes demonstrated in the short follow-up period will be sustained, particularly those of attitude and practice regarding feeding DGL Vs to children. It is significant that plans for expansion are being discussed by local and state politicians, who were encouraged by the evaluation results. (This is an indication of the importance of evaluating interventions in influencing political decisions.) Key elements of success were similar to the Bangladesh experience and included the following:

- Central nurseries for high-quality seeds and saplings were established. They were controlled and managed by the community.
- The community participated at all levels and in all aspects of the project.
- Health and nutrition education was designed for relevance to the local context and disseminated by trained local change-agents.

(Note is made that similar results were achieved in the drought-prone, poverty-stricken area of Nigher, where social marketing was a strategic part of gardening promotion [Parlato and Gottert, 1996]).

Vietnam Gardening Project to Increase Production and Consumption of Vitamin A-Rich Foods*

Context and Design. The project was carried out in poor communes in four provinces with known or suspected nutrition and/or vitamin A problems. The provinces represented four distinct agroecological zones of Vietnam. There were five main components of the project: (1) nutrition education; (2) promotion for production of some specific food crops and of nursery garden development; (3) monitoring and evaluation of activities; (4) training and capacity building; and (5) upgrading food analysis capability. Project activities were implemented at the commune level through a network of trained volunteer-educators,

* FAO, 1995.

with backup assistance in IEC and evaluation from international experts.

Results. After 2 years of implementation, success in achieving stated objectives was documented in four of the five main project components; the least success was registered in the food analysis component. Success was documented by both process indicators, reflective of improved household food security and nutrition (FAO, 1995), and biological indicators of health and nutrition, which demonstrated decreased xerophthalmia and morbidity from acute respiratory infection and diarrheal disease (English et al., 1996).

This is one of the few gardening projects that attempted to document health benefits by monitoring morbidity outcomes. It is an important demonstration that health benefits accrue from successful gardening projects that are associated with increased micronutrient-rich food consumption. Skeptics have only had information from poorly evaluated gardening projects or from controlled DGLV-feeding projects (e.g., de Pee et al., 1995) that failed to demonstrate changes in relatively insensitive biological indicators of incremental changes in nutritional status (see discussion earlier in this paper). These indicators were sometimes used to assess changed vitamin A nutriture in populations in which mean preproject nutriture was not deficient (Brown et al., 1989; Bulux et al., 1994), or in which other potential confounding factors exist (de Pee et al., 1995; Solomons and Bulux, 1993). Nevertheless, it is impractical, expensive, and unnecessary for future large-scale gardening interventions to use morbidity indicators for project evaluation.

The success and feasibility of the Vietnam project has encouraged efforts for national expansion. The expansion design will strengthen critical elements identified in the original project and add elements that had been identified as promoting sustainability. These elements include: (1) training a cadre of indigenous trainers; (2) revolving credit and income-generating schemes; (3) locally available resources for special nutritional rehabilitation of malnourished children identified in the intervention area; (4) community-based monitoring and evaluation of the program; (5) strengthening community nursery gardens; and (6) strengthening the primary health care (PHC) role of the volunteer educators and their links with PHC centers. (It should be noted that at the expansion stage, few other horticultural projects have planned such an integrated, cross-sector-linked approach.)

Other Gardening Projects. In the Philippines and in some Central American countries, household gardening is traditional. In such contexts, it is noteworthy that social marketing strategies may still be needed to sustain interest and assure benefits to targeted land- and resource-poor families (in the Philippines, see Florentino et al., 1993) or to improve cost-efficient operations to

maximize household food-security benefits (in Honduras and Nicaragua, see Marsh, 1995).

Lessons Learned from Successful Gardening Projects

- Advocacy is needed at all levels to increase awareness of affordability, feasibility, and potential household-specific benefits from micronutrient-rich gardening.
- The availability of resource support, education, and training for low-cost gardening close to community operations is critical.
- Commitment of *local* NGOs and other local private and government technical resources and monetary assets are needed before expanding projects at the national level.
- A focus on women in all aspects of garden management and training in product use, including nutrition training, enhances empowerment and decisionmaking that maximize household food security and child-health benefits.
- A simple information-gathering system is needed for systematic community monitoring to resolve, in a timely manner, the ongoing and evolving problems that otherwise could constrain progress and limit gardening success.

Small Animal Husbandry and Fish Production to Increase Household and Community Availability of Preformed Vitamin A Sources

Attempts have been made to foster small-scale animal husbandry and fish production as a means of improving household dietary quality, including vitamin A nutrition. This was one of the thrusts of the applied nutrition programs of the 1960s and 1970s. These programs were short-lived in many areas, generally for reasons that pertained to a lack of resources to discourage poachers and predators (for example, to manage snake infestation in local fish ponds) and assure consumption of the products by poor, high-risk households. In Asia, fresh fish and shellfish, as well as dried whole fish, are available in local markets. When affordable, they are common recipe components (Philippines, National Nutrition Council, 1995). Fish are also to be found—even by the poor and landless—along unprotected rivers, and are available seasonally in tropical areas when monsoon rains overflow rivers and carry fish into the rice fields. Although fish flesh is not a rich source of vitamin A, fish liver is a concentrated source. In societies where fish is culturally acceptable and available, eating small fish whole can significantly contribute to vitamin A intake. Small fish can be cultured in household or community fish ponds. Again, the major constraint to consumption of homestead-produced animal products by the poor is their monetary value, which favors selling over consumption.

In Thailand, where communities are emerging into moderate affluence, promotion of household and community rearing of chickens and ducks has been successful and has the potential for expansion (Wasantwisut et al., 1995). These programs, however, should be accompanied by appropriate social marketing to facilitate household consumption of at least some of the vitamin A-rich products —liver and egg yolk, for example—by at-risk groups. Links are possible between rearing and small-scale processing efforts by local entrepreneurs for production of inexpensive, vitamin A-rich by-products, such as liver chips, that are readily accepted for child feeding. In several Asian countries, chips from many different products are traditional, inexpensive snacks that are regularly purchased by children from street vendors. These items and similar community-generated products could be linked, for example, to school feeding programs in poor villages in order to stimulate local agricultural and economic development. Such an initiative is planned by the government of Indonesia (Soekirman and Jalal, 1996).

In Central America, poultry husbandry, as well as some intermediate and large animal husbandry—when affordable, considering that they demand greater feed and health care inputs—are added to traditional gardens, providing food products for household consumption (such as eggs, meat, and milk), as well as marketable products (Marsh et al., 1995).

To summarize, successful efforts to adjust food consumption and production behaviors require social marketing methodology to strengthen behaviors favorable to good feeding practices in vulnerable groups. As noted above, modifying maternal behaviors in a baby's first year of life to feed the child DGLVs has not consistently yielded to social marketing techniques. Acceptable alternatives for this high-risk group should therefore be considered. For example, where available, small additions of red palm oil (Rukmini, 1994) or buriti (a traditional, beta-carotene-dense local crop in the Amazon region; see Mariath et al., 1989) to carbohydrate-rich paps and gruels can top off breast milk's vitamin A contribution toward meeting vitamin A needs in late infancy.

Multi-Mix Complementary and Weaning Foods

The significance of micronutrients, particularly beta-carotene, in complementary and weaning foods was recognized two decades ago (Graham et al., 1981), but it has captured the important critical attention it deserves only recently (Brown et al., 1996). Past emphasis was on adding vitamin and mineral premixes to cereal-legume mixtures. This is a viable approach when mixtures are centrally processed (Hofvander and Underwood, 1987), but few efforts to produce nutritionally adequate, safe, affordable multimixes at the community, national, or international levels have been sustained. INCAPARINA, developed and marketed in Guatemala, is one notable exception; there are a few others. Lessons learned from past failures in these ventures should provide cautious

guidance to future centralized efforts—private or public—to produce safe processed products that the poor can afford (Motarjemi et al., 1993).

Genetic Selection and Engineering to Improve Vitamin A Activity of Vegetables and Staple Crops

Breakthroughs in genetic selection and engineering have already provided high beta-carotene varieties of carrots. The potential for similar augmentation of the provitamin A activity of other native and widely cultivated food crops has not been exploited. These crops include some basic cereals such as yellow maize varieties and wheat (Graham and Welch, 1996). Bread and yellow pasta and noodles made from natural beta-carotene-enriched wheat have the potential for wide acceptance because their nonwhite color is not an issue. There is even potential for introducing beta-carotene into some varieties of rice where yellow rice is traditionally consumed (for example, saffron is added to rice dishes in many Muslim societies). Varieties of tubers and their young tender leaves—sweet potatoes and vine plants, such as yellow squash and pumpkin—also have potential for genetic selection for provitamin A activity (E-Siong et al., 1995). Constraints encountered include some changes in the texture, taste, and cooking qualities of new varieties that may limit community acceptance. In addition, these genetically selected or engineered varieties sometimes require greater resource inputs, rendering them more costly to produce, and thus decreasing their chance of adoption by poor farmers. Social marketing methodology to facilitate acceptance is needed to introduce non-traditional varieties with unfamiliar characteristics.

Genetic engineering to enhance provitamin A activity of staple food varieties is worthy of support as a potential sustainable solution to the VAD problem among low-income populations. This is a long-term strategy, however, requiring a large dollar investment for R&D. It is an approach suitable to regional agriculture development centers, but of limited potential for communities. It is not a strategy, therefore, that is expected to contribute immediately to overcoming VAD. Faster returns can be expected from genetic screening for provitamin A content of familiar vegetable and fruit varieties and from seeking out traditional, area-specific crops that contain high levels of beta-carotene but are disappearing or underutilized (NAS, 1975; NRC, 1989; Reddy and Vijayaraghavan, 1995).

Can Vitamin A Nutriture Be Improved by Feeding Plant Sources of Provitamin A?

Elimination of VAD within the next few years—a global goal to be achieved in the years that remain to the end of the decade—and sustaining adequate national vitamin A nutriture in the more than 75 countries that now have at least a moderately severe public health problem (WHO, 1996a) will depend

largely on the use of available natural plant foods that contain provitamin A. The prohibitive cost of production or purchase of animal sources for poor families and the limited feasibility of universal vitamin A fortification lead to this conclusion. DGLVs are generally the richest available sources of provitamin A, and the least expensive (Booth et al., 1992). Nevertheless, carotenoids from DGLVs, because of the fibrous, cellulose-rich embedding matrix of chloroplasts, are less bioavailable to humans than those from the chromophore-associated matrix of chromoplasts found in yellow and orange fruits and vegetables. This well-known difference was reviewed in the mid-1960s by an FAO/WHO Expert Group convened to consider dietary requirements for vitamin A. Because of the wide variation in absorption from a variety of yellow and green vegetables (1–88 percent), a middle-ground value of 33 percent, of which half was bioconvertible to retinol (based on animal studies of beta-carotene), was recommended. Recognizing all of its limitations, the carotenoid:retinol bioavailability (absorbed + converted and available for tissue utilization) ratio agreed upon for beta-carotene was 6:1; for other provitamin A carotenoids, it was 12:1 (FAO/WHO, 1967). Through the ensuing years, these ratios have continued to be recommended in evaluating the retinol equivalency (RE) of diets throughout the world (Bieri and McKenna, 1981; FAO/WHO, 1988; IOM, Food and Nutrition Board, 1989).

Infants and young children between 6 and 36 months of age have the capacity to eat sufficient green-leaf products (about 40 g minimum), based on the recommended conversion factors (Rahman et al., 1992). In practice, however, DGLVs are seldom fed to children under 3 years of age as the sole dietary RE. REs are obtained primarily from preformed breast milk retinol during early complementary feeding; they are increasingly supplied by mixtures of fruit and vegetable additions during late complementary feeding and in postweaning diets (Zeitlan et al., 1992). During complementary feeding, the milk fat and bile salt-stimulated lipase in breast milk facilitate carotenoid bioavailability (Fredrikzon et al., 1978). Absorption from fat-poor, postweaning diets of deprived children, however, may limit the capacity for the carotenoids from some plant sources to fully meet vitamin A needs (Jayarajan et al., 1980).

Questions were recently raised by a well-designed, controlled study of lactating Indonesian women as to whether carotenoids from DGLVs are sufficiently bioavailable to improve vitamin A status (de Pee et al., 1995). A between-meal supplement was given that contained DGLVs, either an enriched wafer or placebo control wafer. Worm infestation was common but remained untreated. Both positive intervention regimens contained an equivalent amount of beta-carotene (3.5 mg), and each contained fat (7.8 g with DGLVs and 4.4 g with wafers). Blood and breast milk retinol and blood beta-carotene levels were unresponsive to the DGLV intervention, but responsive to the enriched-wafer supplement. The data were interpreted to indicate that DGLV carotenoids were not bioavailable. Alternative explanations suggested by readers included parasite

loads, sufficient meal-fat content, initial vitamin A status, and the like, and were refuted by authors of the report (Reddy et al., 1995).

Only a portion of the Indonesian women studied were marginally, if at all, deficient. A subanalysis of data from the women in each of the three groups showed that all responded; the enriched-wafer group responded significantly more than the other two groups, whose responses were not significantly different (de Pee et al., 1995). Serum retinol levels of the DGLV-supplemented group, however, were twice those of the control-wafer group, although 50 percent lower than the group fed enriched wafers. This suggests that bioconversion of DGLV provitamin A carotenoids had occurred among women with the lowest serum retinol levels, although the authors attributed this to regression toward the mean. Animal studies, however, confirm a modulating role of vitamin A status on intestinal carotene dioxygenase activity (van Vliet et al., 1993; Villard and Bates, 1986); that is, efficiency of bioconversion is stimulated by deficiency. The true mark of vitamin A status is total body stores. Marginally deficient Indonesian women, therefore, may have efficiently converted DGLV carotenoids and incrementally increased their total body stores, while showing only nonsignificant increments in serum and breast milk. Among nondeficient women, bioconversion may have been less, allowing higher circulating beta-carotene to circulate in the blood while improving already sufficient stored vitamin A by a small increment that was not detectable by the indirect indicator used to signal body store change (modified relative dose response, MRDR). RDR and MRDR measurements are relatively insensitive in determining stores when they are above the critical level indicative of impaired function (Underwood, 1990a).

Thirteen of sixteen epidemiological studies in children reviewed by de Pee and West (1996) found an association, when VAD preexisted, between carotenoid intake from food sources, including DGLV, and improved vitamin A status. These studies showed positive response in clinical and/or biochemical indicators of vitamin A nutriture. Indeed, in a rehabilitation center in south India, even children with xerophthalmia (not keratomalacia) were relieved of clinical deficiency by feeding DGLV, exclusive of vitamin A supplement (Venkataswamy et al., 1976). These epidemiological studies were not as rigorously controlled as the Indonesia study in adult women, and it had design and methodological flaws as noted by de Pee and West (1996).

Nevertheless, a controlled community study equal in rigor to that of de Pee was carried out in Indonesia among 3- to 6-year-old children living in an area of Sumatra where VAD is common (Jalal et al., 1997). Meals and snacks that varied in beta-carotene levels (from DGLVs and red sweet potatoes) and in fat content were supplied at midday for 3 weeks. Some children were dewormed prior to the 3-week feeding trial. Significant improvement in serum levels of retinol followed the addition of vegetables that contained beta-carotene (750 RE/day was the highest level fed). Extra fat (highest level fed was 15 g) and deworming also caused serum levels to increase independently to a similar extent.

The three interventions—extra vegetable carotenoids, fat, and deworming—were additive. Children whose preintervention serum levels were lowest (<0.70 mmol/L) showed the greatest rise in blood retinol levels in each treatment group, and the effect of adding dietary fat was greatest when accompanied by deworming. This study supports the conclusion that vegetable-food-based interventions in vitamin A-deficient areas can successfully improve vitamin A status, particularly when dietary fat levels are also increased sufficiently and helminthic infections are controlled. The programmatic implication is that a concurrently implemented mix of provitamin A, food-based, and public health interventions are best for improving vitamin A nutriture.

Additional research in VAD-endemic areas is clearly warranted to refine our understanding of the factors associated with carotenoid bioavailability from local food sources. Precise quantitative methodologies that measure tissue stores—stable isotope dilution techniques, for example—may be needed to verify bioavailability and changed vitamin A status in some of the studies. These research activities, however, should not deter support for intervention programs to increase provitamin A consumption, including use of DGL Vs, because the weight of epidemiological evidence indicates this "works" to improve vitamin A nutriture.

Fortification

The potential for vitamin A fortification of centrally processed basic foods and/or condiments is attractive because it would require little modification of food behaviors. Remarkably rapid success has been seen with this approach in the global campaign to control iodine deficiency disorders (IDDs) through iodine fortification of salt. There are some lessons from IDD control experiences with fortification that have implications for vitamin A fortification interventions, particularly in the area of IEC and social marketing. A series of publications that review the theoretical, operational, and regulatory aspects of fortification interventions has recently become available for reference (Lotfi et al., 1996; Nathan, 1995; Nestel, 1993).

Vitamin A-Fortified Sugar in Guatemala: A Successful National Experience

Context. Xerophthalmia is not a public health problem in most of the countries of Latin America, including Guatemala, but low dietary intake of vitamin A and low serum retinol values are prevalent. Most refined sugar is processed within the country by a few producers and, except for some areas where a crude, local sugar is preferred, most of the population consumes refined sugar. There is a relatively narrow range of daily sugar intake across the age spectrum. In the 1970s, Guatemala began fortifying sugar with vitamin A, even though

there was objection from some professionals to the use of sugar as a vehicle for a public health nutrient-deficiency control program. During the start-up period, producer commitment to fortification without a price increase to consumers was mandated by the government. Extensive evaluation was built into the initial program to document biological effectiveness and process successes. This resulted in one of the most successful, best-documented national control efforts through fortification yet witnessed in a developing country (Arroyave et al., 1979).

The initial venture, however, was not sustained. Political and economic constraints, including dependency on foreign exchange to purchase vitamin A during a period of economic crisis, halted the program. During this period, VAD reappeared because other VAD control interventions had not received national attention. The fortification program was reestablished around 1990, in part because of heightened global and national political and private sector awareness—and sensitivity—to the consequences of the deficiency problem. The revitalized program was adjusted in accordance with the lessons learned in the initial experience to increase chances for sustainability. Among the measures included were the provision of cost-recovery incentives to the private producers and the creation of a sense of social responsibility among them. A social marketing effort was mounted to create and maintain consumer demand, political visibility, and social responsibility. Global commitment to eliminate VAD as a goal of the decade was made by Guatemalan political leaders who attended high-level international meetings on micronutrients, including the Summit for Children in 1990, the Conference on Hidden Hunger in 1991, and the International Congress on Nutrition in 1992. These meetings raised awareness of the political, economic, and health consequences for national and human capital development of allowing micronutrient deficiencies to persist. The endorsement of a time-bound (year 2000), international goal for eliminating VAD was a useful "lever" in Guatemala to revitalize and maintain political commitment to a national micronutrient program that had been found to be biologically effective. The technical experience with sugar fortification is codified in a series of recently available manuals (Arroyave and Dary, 1996).

Results. The most recent nationwide Guatemalan VAD survey, in 1996, revealed that the prevalence of low (< 0.70 μ mol/L) serum retinol levels has decreased in the 5 years since the program was revitalized (Delgado and Delrue, 1996). Guatemala is now classified by WHO criteria as having a moderate, rather than severe, VAD public health problem (WHO, 1995a, 1996a). Sugar producers are committee to continue fortification, which they now view as their social responsibility.

Success in the Guatemalan sugar fortification program has encouraged replication in other Latin American countries—Honduras, El Salvador, Ecuador, and Bolivia, for example—and it is being pursued in some countries in other

regions where the context for sugar fortification is similarly promising. The major remaining problem is the variability in quality assurance of the fortified product at the production level. A technical solution exists and needs to be applied: upgrading machinery to ensure uniformity in bulk-mixing of the premix containing vitamin A.

Indonesian Experience with Fortified Monosodium Glutamate: A National Failure

Context. Based on successful project experience in the Philippines (Solon et al., 1979), Indonesia began a project to fortify monosodium glutamate (MSG), a condiment consumed widely every day, even by the poor, in relatively uniform and limited amounts. As in the Philippines, and in Guatemala with sugar, the selection of MSG as the vehicle to fortify with vitamin A to control a childhood nutrient deficiency was controversial. Many professionals were skeptical of the safety of consumption of MSG by young children as part of a public health program (HKI/DOH, 1986), although they acknowledged the need to provide vitamin A to poor children. Nonetheless, the pilot project, in cooperation with the somewhat cautious major producer in the private sector, moved forward with the expectation that a national program would be achieved rapidly. Concurrent with pilot field evaluations, safety questions were addressed to allay professional and political concerns (HKI/DOH, 1986).

Results. Community-based, controlled intervention trials demonstrated that the fortified product was acceptable, affordable, and biologically effective (Muhilal et al., 1988a,b). Efforts to expand program coverage stalled, however, when color changes (yellowing) occurred that manufacturers feared would jeopardize sales. Although political objections to program expansion had been overcome, additional technical development work was necessary, which prolonged implementation of a proposed national program and increased R&D costs. In spite of efforts over more than 15 years to overcome constraints, a national program was not achieved. Indonesia has turned to other, less technically bound vehicles for fortification, such as noodles and margarine. (Vitamin A-fortified noodles are also being promoted in Thailand and some other Asian countries.) In addition to the lessons learned about technical factors that contributed to the failure of the MSG-fortification program, the extended time and effort were devoted to overcoming professional concerns about a controversial vehicle; forming productive, trusting partnerships between government and private business; and generating political will (Tilden et al., 1996).

The Philippines Experience with Fortified Margarine: A Promising Government and Private-Sector Partnership

Context. A recent collaborative venture between the Philippine government and the private sector has produced a vitamin A-fortified margarine that is now widely promoted with government endorsement—an "acceptance seal." Although the program is young, indications are that it will be sustainable because government-industry alliances have been established, marketing principles followed, and consumer demand generated through a social marketing program.

Results. Biological effectiveness—an increase in serum retinol—was demonstrated in a 6-month, placebo-controlled trial in one province (Solon et al., 1996). Evaluation of biological effectiveness on a national scale is not anticipated, because this is only one of a series of national interventions to control VAD. Inferences for potential *national* impact are made from the controlled field trial. Nevertheless, evidence will be needed to show sustained market selection of the government-approved fortified product over the competing unfortified product by disadvantaged high-risk households when the choices are freely available.

Other Fortification Efforts

The examples cited above are only a few of a multitude of projects currently under way to seek out and fortify technically promising food and condiment vehicles with vitamin A in a country-specific context. These efforts include fortification of staple products such as vegetable oils and cereals. Rice incorporating fortified, simulated rice grains (Flores et al., 1994) and wheat including nutrient-rich premixes are being tried in some countries. Double and multiple nutrient fortification strategies are in active R&D, because there is potential for adverse nutrient interactions that will affect stability in some mineral and vitamin mixtures (vitamin A and carotenoids, for example, are readily oxidizable). These interactions can be minimized, but at increased product cost that has implications for affordability in public health programs. In countries with VAD, multinutrient product fortification—such as the addition of combined iron/vitamin A/iodine—may be difficult to achieve at prices affordable for public health programs.

Food-to-Food Fortification

Opportunities exist for household-processed, food-to-food fortification of complementary and weaning foods that take advantage of traditional home and

community preservation practices. For example, the potential for micronutrient retention in traditional sundried products (Linehan et al., 1993), such as DGLVs and yellow-colored fruits (such as mango and papaya) and vegetables (including pumpkin, squash, and carrots) can be maximized. In Haiti, a community-level solar-drying technology program focused on women was successful, popular, and became an income-generating activity. After the initial project funding terminated (Linehan, 1994), there was public demand for continuation of the program, and its popularity as an NGO enterprise for women expanded to the Dominican Republic. Other traditional household procedures that offer an opportunity for safe preservation and preparation of seasonally available and perishable vitamin A-rich products should be sought through local focus groups. Some situations may require only the availability of simple food grinders or sieves. Strengthening beneficial traditional household practices could substantially enhance the micronutrient content of the usual, nutritionally poor paps and gruels for the household complementary feeding and postweaning diets of young children. The use of such preservation practices during periods of seasonal glut, as in the cycle of mango production, could carry vitamin A-rich food sources into periods of scarcity. Attention must be given, however, to hygienic home-processing practices in the preparation of complementary foods (Motorjemi et al., 1993). Efforts are warranted to probe potential avenues for fortification at the community and household levels together with production-oriented, food-based strategies that focus on women.

Lessons Learned from Fortification Experiences

Fortification is an attractive, potentially sustainable, long-term solution to VAD in countries that have reached at least midstage in the development of their food industry and distribution system. Private sector cooperation and partnerships with government and other stakeholders are essential to initiate and sustain programs (MI/Keystone Center/PAMM et al., 1996). Lessons learned from past failures, however, should guide national decisions to undertake fortification programs. In developing countries with rudimentary food industries, careful analysis should precede any decision to use limited public resources for fortification as opposed to other potential interventions in an "either/or" choice for VAD control. In this context, several years may be needed to launch a viable national fortification program. The criteria to be used to determine start-up and maintenance costs, cost-effective coverage of vulnerable groups, and the cost of sustainable product-quality assurance are a few additional considerations. The selection of a suitable vehicle must consider political, as well as technical, issues.

Contrary to the view that behavior change is not needed in the recipient population where there is product choice, the creation of demand for fortified over unfortified products will require well-designed social marketing strategies.

Mandated national, universal fortification of a single food item, advocated by international organizations in the iodination of salt, will be difficult to enforce for vitamin A when no appropriate universal vehicle is identified. Where critical elements for sustainable programs can be assembled, fortification can benefit producers, consumers, and government through cost-effective control of VAD, but unless critical elements are in place, ventures into fortification can result in substantial losses and program delays. These decisions should be made at the national level, but only after political and social support has been created. Appropriate international assistance should be available as requested by national governments after this support has been created. External assistance may best be directed toward short-term capital investment for product-quality assurance and monitoring, rather than for ongoing operations and marketing activities that will require national financing for sustainability.

Emergency and Food-Aid Programs

For emergency and food-aid programs, foods fortified with vitamin A are critical. Lessons learned from the inappropriate use of unfortified skimmed milk to feed severely malnourished children, which precipitated xerophthalmia, were well-documented many years ago in Brazil (do Vale Pereira et al., 1966). Additional anecdotal reports of similar experiences elsewhere stimulated WHO and the World Food Program (FAO, 1977), as well as other bilateral and relief agencies, to fortify products for infant and young child feeding with vitamin A in emergency, food-aid, and supplemental feeding programs. Acute refugee and emergency-relief efforts in VAD-endemic areas require special attention to micronutrient supplementation. For vitamin A, this means a high-dose supplement for children (WHO/UNICEF/IVACG, in press), followed by fortified food rations that reach the entire unsettled population.

Supplementation

National Delivery Systems

Periodic distribution of high-dose vitamin A supplements, either to all children of a specified age range or to targeted high-risk groups, has been the most widely applied intervention with proven effectiveness for treatment, prevention, and control of VAD. Guidelines are available for the use of vitamin A supplements for these purposes (WHO/UNICEF/IVACG, in press). Experiences with periodic high-dose programs were summarized in 1987 (West and Sommer, 1987) and updated in 1994 (Gillespie and Mason, 1994). The conclusion of these reviews was that the high coverage necessary for biological effectiveness

for VAD control in the population (65 percent minimum) was not sustainable through iterative (4- to 6-month) vertical programs. Targeted supplementation was potentially more cost-effective where there is high utilization of health and/or community service. Because targeting is a passive program—deficient children are not actively sought—many at-risk children in community settings are missed (Berger et al., 1995). The cost-effectiveness for each affected child in targeted programs has thus been questioned. Nonetheless, almost all countries with VAD will continue to have some use for targeted delivery of vitamin A supplements, including treatment of xerophthalmia and severe measles, PEM, and persistent diarrhea; emergency and refugee situations; and a variety of recalcitrant settings where a shortage of foods containing vitamin A persists, such as isolated or remote, drought-prone, poverty-stricken areas.

Failure to achieve sustained high coverage through vertical universal delivery systems and the limited utilization of health/community service facilities in some targeted programs has led to alternate approaches for supplement delivery. In the Philippines (and some other countries), for example, delivery of high-dose capsules is confined to biannual "special days" that are linked to providing other deficient micronutrients as well (UNICEF-Manila/HKI, 1996). Among infants between the ages of 9 and 12 months in India, supplement distribution is encouraged during measles immunization (India, Ministry Health and Family Welfare, 1995), and every 6 months thereafter through feeding and/or growth monitoring programs. In Bangladesh, coupling low-dose supplements (25,000-50,000 IU) with immunizations scheduled throughout the first year of life, and at special-event days thereafter, is encouraged to improve coverage (Karim et al., 1996). In Indonesia, following a social marketing campaign to create increased demand, trained health volunteers were used to increase the capacity of the service delivery system to meet the demand; they were subsequently used for face-to-face education and promotion of vitamin A (Reis et al., 1996). Experiences with these alternate prophylactic approaches have substantially improved periodic supplement coverage at reduced costs (Arhin et al., 1993). Other countries are beginning to implement one or more of these modified approaches and reported similar high-coverage success. It is too early to determine if the broad coverage attained will be sustained. If national strategies are planned to concurrently begin to phase in more sustainable food-based approaches, the high coverage achieved through special event days and other specially created delivery systems should not be required beyond 2 to 5 years.

The Experience of Northeast Brazil with Community-Supported Supplement Distribution

Context. It is worth reviewing the experience of Brazil with high-dose supplementation. The program was directed toward a poverty-stricken area in

the northeast, where malnutrition, including clinical and subclinical VAD, is reported. Affordable animal sources of vitamin A are scarce in the northeast, and diets are generally low in provitamin A carotenoids, both because of limited production and seasonal availability in this water-scarce environment. In addition, there is a strong cultural aversion to the consumption of leafy green vegetables. In this context, universal vitamin A supplementation was selected as the appropriate, *area-specific* intervention. (Because the problem is not as serious in other, relatively affluent, parts of this large country, it has been difficult to draw national professional and political attention and resources to an area-specific problem in the less-developed regions.)

Intervention Design. In Caruaru, a mayor and city council that are conscious of the public health, with the health department and support from local academicians, determined that a communitywide, biannual distribution campaign was appropriate and affordable. The campaign had the full support, including financial assistance, of both the local political and business communities. It was organized entirely around specially trained community volunteers and was supported by the local university nutrition department with biological (serum retinol and relative dose response [RDR]) evaluation of effectiveness in representative subsamples of children before and during each of five subsequent distribution rounds.

Results. Over 90 percent coverage was sustained at each of five successive distribution rounds (over a period of nearly 3 years). Serum retinol distribution curves shifted toward the right in the left portion, and stability was achieved in the community after the third distribution. (Earlier work had demonstrated that a stable distribution curve reflected adequate vitamin A in the population; Flores et al., 1991). The program survived a change in political administrations. It was expanded into a statewide program and integrated into PHC, linked to periodic immunization initiatives (IVACG, 1992). Success was ascribed to creating consumer demand for the program through the active participation of local volunteers, business leaders, and political figures. Also, external assistance was only required for provision of the vitamin A supplement. Even the social marketing program was developed and financed locally.

The Experience of Bangladesh with an Immunization-Linked, Prophylactic Supplementation Program for Infants

Context. Bangladesh has suffered from a high prevalence of xerophthalmia in preschool children, in spite of biannual distribution of high-dose supplements since 1973 (Cohen et al., 1987; Underwood, 1990b). Breastfeeding is nearly universal, prolonged, and protective from xerophthalmia

(Mahalanabis, 1991), but because of maternal malnutrition, it is not sufficiently protective from depletion of vitamin A stores in late infancy (Underwood, 1994a). To combat this problem through prevention, the government recently adopted a program linking the distribution of vitamin A supplements to immunization contacts for infants at about 6, 10, and 14 weeks and 9 months. The rationale was that piggybacking distribution of vitamin A supplements onto expanded program on immunization (EPI) contacts would take advantage of the successful, broad coverage achieved through EPI to maintain vitamin A status throughout infancy (WHO, 1994). In theory, this approach could provide broad protection of stored vitamin A above a critical level for infants that were breast-fed by VAD mothers until they can be reached by other ongoing distribution programs (WHO/IVACG, 1992).

Results. Reports of increased prevalence of bulging fontanel at doses of both 25,000 IU (Baqui et al., 1995) and 50,000 IU (de Francisco et al., 1993), apparently linked to cumulative dosing, caused professional concern and political controversy over whether the program should continue. Follow-up revealed no evidence of lasting consequences among infants who experienced bulging (van Dillen et al., 1996). Nonetheless, program adjustments were made to dose only at 6 and 14 weeks with 25,000 IU. Consensus was then reached among scientists and politicians to continue with the modified national program. Coverage from 6 months through the preschool years is now achieved through biannual national "special days" for distribution. (A WHO-sponsored multicountry—India, Peru, Ghana—random, controlled community trial of safety and efficacy using this approach is expected to be completed in 1997/1998.) These new distribution approaches are reported to have substantially increased supplement coverage in Bangladesh (Karim et al., 1996). Follow-up surveys will be needed to substantiate sustained high coverage and to demonstrate biological effectiveness in nationwide efforts to reduce the prevalence of VAD, a goal not achieved in over two decades of supplement distribution using other strategies.

Possibilities for Low-Dose, Community Supplementation

For more than two decades, prophylactic use of vitamin A supplements focused exclusively on high doses given periodically—100,000 IU for infants 6 to 12 months old and 200,000 IU thereafter. The 200,000 IU dose given to children over 1 year of age protects longer, at least for 4–6 months, than 100,000 IU (Humphrey et al., 1994). These dosage levels, given at 4- to 6-month intervals, rarely produce significant acute toxicity symptoms beyond the ages of 6–12 months (Florentino et al., 1990; West et al., 1992), even when multiple doses are accidentally given (Rosales and Kjolhede, 1993). Among the several controlled, randomized community trials, however, the greatest impact on mortality

reduction was achieved with frequent daily intakes of low doses through fortified MSG (Muhilal et al., 1988a,b) or weekly 8,000 IU supplements (Rahmatullah et al., 1990). High-dose supplement distribution should be controlled and monitored, usually through the health infrastructure, to reduce risks of misuse (for example, to pregnant women) and multiple dosing (incident-linked disease targeting, for example). Low-dose distribution (10,000 IU and less), in contrast, could be safely managed through community systems such as trained volunteers, mothers' groups, and child-to-child programs, and could include availability through local pharmacies or community medicine kiosks. Such low doses are safe for community distribution and management, even for fertile women (WHO, 1996b). An ethnographic study recently completed among night-blind pregnant women in Nepal found that about 25 percent purchased a "goti" (low-dose, 5,000 IU preparation) from the local medicine shop or market pharmacy on their own initiative (Christian, 1996). Although the prices of these preparations were found to be quite low in Nepal (about US $0.02 for three to six tablets), they were an economic constraint for some (Christian, Johns Hopkins University, School of Public Health, 1996, personal communication). Government subsidization of low-dose community-managed programs might be necessary, although this investment would be modest compared with the high costs for the delivery of safe, large-dose supplements.

The feasibility of sustaining frequent, low-dose supplement programs that reach vulnerable groups on a weekly or monthly basis has been questioned. The management scheme Rahmatullah et al. (1991) used achieved over 90 percent coverage with a year of weekly delivery through the use of part-time, trained community health volunteers (CHVs). Key features of this model included:

- Nominations of CHVs were community-based and selection was based on performance.
- Weekly supervision and feedback was based on problems encountered by CHVs.
- Distribution coverage responsibilities were limited to a convenient area.
- Flexibility was employed to adjust work schedules to fit the other family responsibilities of the CHVs.
- There was strict accountability for self-selected work schedules.
- Support was given for CHV-initiated referrals to the health care establishment (this created community recognition, credibility, and prominence for the CHVs).

The efficiency of community-managed, frequent low-dose vitamin A supplementation as an alternative to high doses has not been adequately tested. There is an urgent need to test this approach because increased evidence has accumulated that under supervised conditions, weekly dosing with iron is effective

in prevention and control of iron deficiency. Dual weekly supplement delivery to overlapping vulnerable groups could significantly reduce future micronutrient control costs.

Lessons Learned from Supplementation Programs

Prolonged experience in India and Bangladesh with vertical, universal supplement distribution programs convincingly shows that xerophthalmia cannot be controlled with this strategy, for operational rather than biological reasons. In contrast, the biannual "special days" approach for nationwide distribution, especially when combined with social marketing, has dramatically improved coverage. These "special days" programs, however, have not been in effect long enough to evaluate their sustainability. Sustainable programs of this nature certainly depend on continued political commitment, which may wane as other, more visible and politically sensitive, health needs are given higher priority. As few as three years of high coverage from such distributions may be sufficient to raise vitamin A status, provided that other sustainable food-based programs are established, such as the use of fortified foods and favorable diet behaviors, to take over and maintain adequate vitamin A nutriture. Alternatives for multiple delivery channels for low-dose supplements and cost-effective delivery that is piggybacked on other broad-coverage PHC programs deserve consideration.

Public Health Interventions

As noted in the introductory paragraphs, VAD results from an imbalance between supply and need, and the need side of the equation is increased by disease frequency. Frequent disease episodes are accompanied by undulating patterns of decreased intake and absorption and increased excretion and elevated metabolism (Keusch and Scrimshaw, 1986). PHC, including breast-feeding promotion, immunization, growth monitoring, oral rehydration, family spacing, hygiene education, and environmental sanitation can be entry points for direct and indirect VAD control (Habte, 1987). Disease-control programs, however, can only *contribute to* VAD control; increased vitamin A intake is also necessary. High measles immunization coverage can make a particularly important contribution to VAD control. This was documented in Tanzanian children by the threefold reduction in hospital admission for corneal ulceration associated with improved measles immunization coverage (Foster and Yorston, 1992).

Respiratory infection (ARI) control does not prevent vitamin A deficiency, and providing vitamin A does not protect from pneumonia or reduce pneumonia-related deaths (WHO, 1995c), except for the severity of pneumonia associated with measles (Coutsoudis et al., 1991). Some reports of increased prevalence

of ARI (and some other disease-related symptoms) after periodic high dosing (Stansfield et al., 1993) initially caused alarm, but have other possible explanations, including a heightened disease response that is ultimately beneficial (Fawzi et al., 1995; Underwood, 1994b). Alternately, increased symptom responses may be restricted to adequately nourished children not in need of high-dose vitamin A (Dibley et al., 1996). Control of respiratory infections, however, as with other febrile infection control (Mata, 1992), improves metabolic conservation of vitamin A (Stephenson et al., 1994). When accompanied by programs that increase vitamin A intake, it contributes to at least maintaining existing vitamin A stores (Marinho et al., 1991; Rahman et al., 1996).

Diarrheal disease control contributes to VAD control by indirect effects on appetite and metabolic conservation, especially febrile episodes (Alvarez et al., 1995; Becker et al., 1991). Data are unclear regarding the effect of improved vitamin A status of deficient children on the incidence, severity, and persistence of diarrheal disease (Dibley et al., 1996; Feachem, 1987). Recent reports from closely monitored, random, controlled vitamin A supplementation field trials in deficient children clearly demonstrate a decreased severity of *subsequent* diarrheal morbidity (Barreto et al., 1994; Bhandari et al., 1994). High-dose supplements given during an acute attack of diarrhea are absorbed sufficiently to improve body stores (Reddy et al., 1986), but do not usually alter the course of the acute infection (Henning et al., 1992). Some trials suggest a small effect of supplementation on diarrheal disease incidence (Barreto et al., 1994; Fawzi et al., 1995). Public health measures for diarrheal disease control, therefore, can be expected to enhance the effectiveness of interventions that increase vitamin A intake from supplements or food, but will not replace them.

Evidence is unclear regarding whether deworming alone will improve the vitamin A status of deficient children unless there is also increased vitamin A intake. Ascariasis infections are not consistently reported to interfere with vitamin A absorption (Ahmed et al., 1993; Mahalanabis et al., 1979), but giardiasis infection does interfere (Mahalanabis et al., 1979). VAD Indonesian children reportedly benefited from deworming alone, and the effect was additive when vitamin A-rich foods supplemented the diet (Jalal et al., 1997). Another Indonesia-based study found deworming ineffective in improving vitamin A status without an accompanying high-dose supplement (Tanumihardjo et al., 1996). Ascariasis as well as giardiasis infections also interfere with fat absorption, which may have a particularly adverse affect on food-based carotenoid interventions (de Pee et al., 1995). Worm loads affect absorption of zinc (Marinho et al., 1991), and this micronutrient is needed for retinol-binding protein—as well as other protein—synthesis, critical to retinol transport and utilization. The complex interaction of worm load and vitamin A utilization (Solomons and Keusch, 1981), and nutritional status generally (Mata, 1992), argues strongly for concurrent deworming and improved vitamin A intake interventions to maximize immediate and sustained VAD control.

Lessons Learned from Public Health Interventions for Disease Control

Disease control is an important addition to—not a replacement for—interventions that increase the vitamin A intake of deficient populations. These measures have beneficial spin-offs in the prevention of malnutrition generally, thus increasing their cost-effectiveness in deprived populations (Keusch and Scrimshaw, 1986).

COMPLEMENTARITY OF INTERVENTIONS

Phasing in Vitamin A Interventions

Where VAD remains a public health problem, a mix of interventions is usually needed to meet both the acute need to treat and control health-related, and often irreversible, consequences and to sustain VAD control through affordable means (Gillespie and Mason, 1994). In the short run, especially where xerophthalmia or severe subclinical deficiency is documented, vitamin A supplements will be part of any control strategy and may be distributed universally in time-limited distribution programs such as those discussed above. In Caruaru, three distribution cycles at 6-month intervals stabilized satisfactory vitamin A status in children under 6 years of age. This suggests that 18 months is a minimum time period for phased-in programs that are introduced *concurrently* with universal high-dose supplementation that will replace them and to sustain adequate communitywide vitamin A status in children.

Under some circumstances, a fortification program such as those operating in a number of Latin American countries is the most likely choice for a high-dose supplement-replacement intervention within about 2 years. This short time frame is possible where fortification technology is already established for a widely consumed vehicle—as was the case for the revitalized sugar fortification intervention in Guatemala. (In Venezuela, iron and vitamin A—about 228 RE/capita/day—fortification of precooked maize flour and iron in wheat flour over 2 years led to remarkable reductions in iron deficiency. Vitamin A status changes have not been reported. See Layrisse et al., 1996). In countries where vehicles are still being sought, or where technology is still in the R&D phase, a longer phase-in time for fortification interventions is expected, but the process should be started and receive increased emphasis as feasibility progresses.

Natural food-based, homestead provisioning interventions in India, Bangladesh, and Vietnam, when reinforced through social marketing to increase consumption as well as production, began to show improvement among participating communities within a 2-year period. It is unlikely that natural food-based interventions alone would control VAD in such a short period because of limited coverage and the longer time period needed to instill dietary behavior

change through education and social marketing (Contento et al., 1996). Where there is potential for increased home provisioning among deprived families, this intervention should accompany other interventions that have wider coverage (such as fortification) because they will bring additional household food security to the most needy.

Even social marketing to improve consumption of already available but underutilized DGLVs and fruits, as in Thailand, can bring about behavior change in dietary practices in 2 years, although not in the entire population. This strategy should accompany all other vitamin A interventions, especially those requiring behavior modifications in consumption. The marketing and education messages require frequent reinforcement for several years before changed behaviors can be expected to become embedded in communities.

In Tanzania, experience with expanded measles immunization coverage dramatically reduced admissions for xerophthalmia in a 3-year period. Such dramatic results from immunization-preventable and other infectious disease control measures should not be expected. These programs should be emphasized, however, because of their incremental contribution to the effectiveness of other vitamin A-specific interventions.

The examples of field experience reviewed above represent strong arguments for formulating an overall national control strategy in which interventions overlap, each receiving the degree of emphasis appropriate for the community context and the severity of the VAD problem and a comparable share of the resources available for VAD control. The aim should be to replace universal high-dose supplement use—retaining such supplements to deal with high-risk and recalcitrant situations—within a time frame ranging from 2 to 5 years at a minimum; for most countries with xerophthalmia, a more realistic estimate would be up to 15–20 years (the cases in Indonesia and Tanzania, described earlier). There are important opportunities to establish phase-in schedules for the mix of interventions identified as feasible in a given situation and to establish the degree of concurrent emphasis to be given to each one. The emphasis to be given should be established by the findings of a situation analysis so that preestablished goals can be met within a specified time frame.

Vitamin A with Other Micronutrient Initiatives

VAD seldom occurs in isolation, but within the context of deprivation (Underwood, 1990b), including multiple vitamin and mineral deficits, particularly of iron, iodine, and possibly zinc. It is attractive to conceive of dealing with all of these deficits concurrently. A careful analysis needs to be undertaken, however, to determine where program compatibility exists in the areas of awareness, assessment, analysis of causes, and resources available for solutions. Tables 4-4 through 4-6 summarize some overlapping and divergent areas for

planning consideration. Coordinated strategies are technically feasible (Trowbridge et al., 1993), but infrequently implemented.

Except for iodine, natural food-based approaches are the most logical for integrating micronutrient control programs. Interactions are avoided between potential concentrated-dose incompatibilities among supplements, such as solubility differences, susceptibility to oxidation, and competition for absorption. The situation in IDD control is different, because the deficit is not correctable by simply growing more or a different variety of food in the same iodine-depleted area. Furthermore, there is a proven cost-effective IDD control intervention—universal iodination of salt—that should receive continued support, using oral iodine supplements to control the problem in limited, unyielding situations. Nonetheless, there are areas of opportunity for cost-saving in complementary activities in assessment, program selection and design, and delivery mechanisms to vulnerable groups where micronutrient deficiencies coexist.

COSTS AND BENEFITS

Attempts to make comparative cost/benefit evaluations of vitamin A interventions require many assumptions on both sides of the equation. The *World Development Report 1993* (World Bank, 1993) estimated costs in deaths averted and DALYs (disability-adjusted life years) saved by vitamin A supplement, fortification, and general food supplementation programs (Table 4-7). Irrespective of the difficulty of maintaining high coverage, distribution of vitamin A supplements was the least expensive. Recent innovations in delivery through piggybacking with other public health programs (as reviewed above) may render this approach even less expensive. Whenever food consumed by the target population can be fortified at reasonable cost, fortification can provide the same vitamin A-related benefits as changes in diet, and it is likely to be easier and occur faster. Food supplementation programs are fraught with targeting errors and the replacement of food in the normal diet, greatly increasing their relative cost-benefit ratio. The World Bank report does not attempt to apply dollar values to gardening or social marketing and education strategies.

A project conducted in Nepal attempted a cost-effective analysis of three vitamin A interventions: semiannual capsule distribution, capsule distribution piggybacked with PHC, and nutrition education activities piggybacked with PHC (Tilden et al., 1993; University of Michigan, 1993). Distribution of vitamin A supplements was the least costly, followed by PHC and nutrition education.

Phillips et al. (1994) reported on the costs and effectiveness of three vitamin A interventions in Guatemala: sugar fortification, capsule distribution, and gardening plus nutrition education. This analysis reported cost per high-risk person achieving adequate vitamin A status to be US$0.98 for fortification, US $1.86 for capsule distribution, and US$2.71 to US$4.16 for gardens.

TABLE 4-4 Etiology of Deficiencies of Iodine, Iron, and Vitamin A, Vulnerable Groups for Each Deficiency, and Appropriate Groups for Surveillance Purposes

Category	Iodine Deficiency	Iron Deficiency	Vitamin A Deficiency
Etiology	Geographic	Dietary/increased loss	Dietary/ increased loss
Vulnerable groups	Entire population: Women of reproductive age, infants, and young children	Pregnant/lactating women Infants Preschool-age children Adolescent girls Women of childbearing age	Pregnant/ lactating women >6-month-old infants Preschool-age children
Surveillance groups	School-age children	Pregnant women Preschool-age children	Preschool-age children

TABLE 4-5 Useful Biological Indicators in Surveys to Assess Iodine, Iron, and Vitamin A Status

Indicator	Iodine Deficiency	Iron Deficiency	Vitamin A Deficiency
Diet	x[a](±)	x + knowledge of meal pattern	xxx
Urine	xxx	—	—
Blood	xx	xxx	xxx
Breast milk	xx	—	xxx

[a] Number of "x"s indicates level of importance as an assessment indicator.

TABLE 4-6 Intervention Strategies Applicable for Prevention and Control of Iodine, Iron, and Vitamin A Deficiencies

Strategy	Iodine Deficiency	Iron Deficiency	Vitamin A Deficiency
Food-based strategies	Iodized irrigation/ drinking water? Fortification	Natural foods Quantitative Qualitative Fortification	Natural foods Quantiative Qualitative Fortification
Supplementation[a]	Iodized oil	Iron tablets/syrup	High-/low-dose preparations
Public health measures		+++[b]	++
IEC	+++++++++		

[a] Supplements are often necessary as a time-limited measure where the problem is severe.
[b] Number of "+"s indicates level of importance.

TABLE 4-7 Cost-Effectiveness of Some Vitamin A Interventions

Intervention	Target Group	Approximate Cost (US$)	
		Per Death Averted	Per DALY Saved
Supplementation	Children < 5 years	50	1
Fortification	Entire population	154	4
Food supplement	Children < 5 years	1,942	63
Food supplement	Pregnant women	733	24

SOURCE: Adapted from *World Development Report 1993*, World Bank, p. 82.

Annual fortification costs per person are estimated to range from about US $0.06–0.08 for MSG and corn/wheat flour, US$0.20 for margarine, and US $0.30–0.40 for cooking fat (Lotfi et al., 1996). Arroyave and Dary (1996) estimate the cost of sugar fortification to be about US$0.40–0.84 annually, but up to $10.53 if calculated on the basis of each recovered child—that is, recovered from inadequate to adequate vitamin A status.

The benefit/cost ratio for the pilot HKI Bangladesh gardening project, calculated only in monetary terms for target households and program costs, which underestimates true benefits since many are nonmonetary, was near 1 (0.997; a favorable ratio is considered to be anything above 1). Annual cost for each target family averaged US$39.0. When disaggregated to an individual garden level that included operating costs for seeds and seedlings, crop protection (fencing), and irrigation, US$11.7/year was spent; minus fencing and irrigation, the total was US$3.00/year. Overall, the disaggregated benefit/cost ratio—*only in monetary terms*—was 3.3, a very positive outcome. The national version of the project, working through Bangladeshi NGOs, has reduced costs to an estimated US$8.33/garden or US$1.50/individual (Marsh, 1995).

In summary, all the evaluations of cost-effectiveness reviewed agree that fortified foods or capsule distribution, depending on whether a fortifiable food that is widely consumed by the high-risk group is available, are potentially the least expensive interventions. Although fortified foods are likely to be the more sustainable investment, it has been difficult to identify an appropriate food to fortify in most developing countries. Capsule distribution is a proven, time-limited, cost-effective intervention if coupled with programs that have effective service delivery to target groups and there is a consistent and adequate supply. Promotion of increased consumption and/or production of food is a viable option in most contexts where water supply is not critically short, but requires application of a social marketing methodology to overcome socioeconomic and cultural barriers to behavior changes where benefits are not always obvious. There are many difficulties in quantifying nonmonetary benefits in order to realistically estimate the cost/benefit ratios associated with each intervention. Nonetheless, over the long term, interventions that provide balanced, multinutrient

improvements, such as nutrient-rich natural and/or fortified foods, are most likely to provide permanent benefit to recipients in deprived contexts.

BALANCING APPROACHES TO COUNTRY-SPECIFIC CIRCUMSTANCES

Countries with micronutrient deficiencies at a public health level are usually confronted with the multiple problems of underdevelopment and limited resources to deal with them. Prioritization is essential, not a choice. A series of notable political events, beginning in 1990 with the World Summit for Children (UNICEF, 1990) and the follow-up 1991 conference, Ending Hidden Hunger (WHO/UNICEF/World Bank/CID/USAID, 1991), focused the attention of the participating countries on micronutrient malnutrition. The preparatory process for the International Conference on Nutrition in 1992 (FAO/WHO, 1992) and the country-level follow-up actions have fostered planning for micronutrient deficiency control at the national level, which was virtually nonexistent in many countries before these high-profile political events. National planning is often done collaboratively with international and bilateral agencies because their financial assistance is needed for program follow-up. In spite of donor involvement, it is essential that planning be driven by nationally determined considerations, not driven by donors to achieve internationally set, time-bound goals.

With multiple international and national agencies and NGOs working in micronutrient deficiency control, coordination is indeed difficult. Too often, this is done without adequate input from affected communities because collecting these views takes time and requires personal communication skills and knowledge of local situations that are generally not available at the national and international levels. It is in these areas that local NGOs can make major contributions. Policy and program strategies can be set nationally, but implementation flexibility is needed to take advantage of local situations, particularly in food-based interventions that require behavior change. In reviewing food-based approaches for this paper, merit was found in first developing such approaches at the community and regional level, allowing expansion to occur as success is demonstrated and elements of success are identified and adapted for application to different regional contexts.

Two National Case Studies

Indonesia

Context. Indonesia is a vast nation of multiple islands. Its 180 million people stretch over 3,000 miles across the equator. Up to the 1970s, the country

was plagued by poverty, underdevelopment, and poor health statistics; there were small-scale survey and anecdotal reports of widespread xerophthalmia. National economic resources to launch public health programs were very limited. Increased resources from oil revenues stimulated the economy in the early 1970s. In 1969, Indonesia initiated a series of five-year plans founded on the principles of economic growth, equity, and stabilization. In the 25 years that followed, Indonesia moved from among the poorest of developing nations to among the top in per capita income (Soekirman and Jalal, 1994a; Soekirman et al., 1992).

Late in the 1970s, a systematic assessment was made of the xerophthalmia problem, which was found by WHO criteria (WHO/UNICEF/USAID/HKI/IVACG, 1982) to be of public health significance in 15 of 23 provinces. Intervention strategies were planned that included nutrition education, distribution of high-dose vitamin A supplements, food fortification, and other public health disease-control measures. Emphasis was given to biannual distribution of vitamin A supplements through health service posts. This began as a pilot project in 1972–1973 and was expanded to a national program in 1974. The capsule distribution program, the backbone for national VAD control for 22 years, continues to the present with variable coverage rates across provinces. The community study reported in 1986 (Sommer et al., 1986) that documented decreased mortality risk of treated children in Aceh Province—a province identified in the nationwide prevalence survey to be highly endemic for VAD—prompted increased public and political awareness and resource commitment to vitamin A programs. Nutrition education centered on promotion of DGLV production and consumption and cooking demonstrations by health posts. These educational efforts, often managed by local women's groups (such as PKK, Family Welfare Women's Movement abbreviated to its Indonesian equivalent of PKK), were recently reinforced by a broad social marketing of vitamin A-rich foods. Fortification efforts received attention in about 1980, but it was focused exclusively on vitamin A-fortified MSG, which was found to be technically unsuccessful (reviewed earlier in this paper). No effective national fortification program currently exists.

Results. Although the national survey of 1977–1978 (23 of 27 provinces) has not been repeated, surveys in 15 individual provinces conducted in 1992 suggested that xerophthalmia was no longer of public health significance. A few provinces, however, were still affected. The prevalence of active xerophthalmia declined by 75 percent and that of active corneal disease by 95 percent (Muhilal et al., 1994). By 1994 the problem was controlled in the remaining provinces, which led Indonesia's President Suharto to declare Indonesia xerophthalmia-free (Soekirman and Jalal, 1994a). An unacceptably high prevalence of low serum vitamin A levels persists, however, indicating that *subclinical vitamin A inadequacy remains*.

Conclusions. In about 15 to 20 years, including 10 recent years of accelerated national effort that was further stimulated by political endorsement of international elimination goals, Indonesia has eliminated significant xerophthalmia through interventions that primarily depended on high-dose supplement distribution. Recently introduced social marketing facilitated broadened coverage and reinforced earlier nutrition education efforts. This has contributed to increased public awareness and mobilization. Noteworthy in bringing about this commendable success is the concurrent improved national economic situation, with spin-offs for health service delivery and poverty diminution. The specific reasons for the xerophthalmia decline in Indonesia cannot be ascribed to any particular intervention because of the multiple concurrent health and social changes (Muhilal et al., 1994).

Sustained high political and social awareness of the human and national development consequences of the still prominent subclinical VAD has helped retain support for intervention efforts. VAD-control emphasis is beginning to shift toward fortification programs and the social marketing of vitamin A-rich food. These programs are likely to maintain national vitamin A adequacy because natural food sources are available to vulnerable populations but underutilized, and the food-processing industry is rapidly gaining, and their processed products reaching, an expanding consumer market. Success in overcoming subclinical deficiency will require added emphasis on public health disease-control interventions and poverty alleviation among hard-to-reach, high-risk households. Indeed, it might have taken less time to reach national vitamin A adequacy if a more balanced, mixed-intervention program had been emphasized from the start. Balanced intervention efforts were envisioned in early national planning, but they were not achieved, in part because of Indonesia's stage of economic and social development at the beginning of the program.

The Indonesian experience provides important policy and program lessons, some of which are transferable to other countries that are now beginning micronutrient deficiency interventions.

Tanzanian Experience

Context. Tanzania currently accommodates about 27–30 million people on a land area of about 950,000 sq. km. (Kavishe, 1993). In spite of slow economic and social growth indicators into the early 1990s, the country ranks high on equitable education and social service accessibility. National programs are decentralized to allow decisionmaking, implementation, and management at the district level and below. In about 1982, a xerophthalmia surveillance system was established through sentinel hospitals. Data from this surveillance system, together with some small surveys and clinical trials, called attention to the serious public health problem that affects certain areas and was seen nationally in "at-risk" groups (Kavishe, 1992). Following a participatory process based on

UNICEF's triple-A approach, the government formulated a series of five-year program plans for VAD control in 1985. A mixed intervention package was designed for national coverage, with major emphasis on the *dietary* approach to stimulating production and consumption of affordable vitamin A-rich foods, including red palm oil; public health strategies; and targeted distribution of vitamin A supplements. The supplement program was based on 50,000 IU capsules dispensable in multiple units, as appropriate, through the health infrastructure's Essential Drugs Program, and distributed universally in a few particularly deficient areas. The 50,000 IU supplement capsule allayed the safety concerns of some professionals and allowed flexibility in accurately meeting recommended dose levels for different age groups. Fortification, not immediately feasible as a national control program, was given exploratory emphasis for possible future inclusion in the mixture of national interventions. During the intervention phase that followed, a National Vitamin A Consultative Group (NVACG) was formed under the auspices of the Tanzania Food and Nutrition Center. This multidisciplinary group had both advocacy and technical guidance roles to ensure that implementation of interventions gave balanced consideration to such varied factors as historical precedence, targeting, dietary diversification, supplementation, fortification, IEC, affordability, and issues of sustainability.

Results. An analysis of impact from 1982 to 1990, using the sentinel hospital surveillance system, indicated that the prevalence of active xerophthalmia was on the decline, although still of public health significance. In two divisions where universal distribution of supplements had occurred, an increase in the prevalence of near-adequate serum retinol levels was recorded (Kavishe, 1992). Further achievements were reported to the IVACG meeting held in Arusha in 1993. At the meeting, the NVACG group demonstrated the nationally promoted, community-constructed solar drying units that supported their food-based emphasis, and they reviewed progress in their efforts to find a suitable vehicle for vitamin A fortification (IVACG, 1993).

Conclusions. The Tanzania program provides a mixed intervention emphasis that was balanced from the beginning in identified national and community-specific needs and resources. The program provides elements that allow safe, community-based management. A food-based approach is the backbone of the program, but supplements are given targeted use. The historical tradition of decentralized participatory action—characteristic of the successful food-based projects reviewed above—suggests that in such a contextual setting, much is achievable in a decade, even in countries where national economic, industrial, and social development is slow to occur. (Comparative note is taken of the situation in Kerala, India, where the context is quite similar and where, in contrast to most other Indian states, xerophthalmia is unusual.)

SUMMARY

Vitamin A is now recognized to regulate expression of multiple genes that influence animal health, development, and survival, hence providing the scientific underpinning for historical accounting of its essentiality in the diet of humans. Several million child lives could be saved, morbidity tempered, and sound vision preserved by ensuring adequate vitamin A nutrition among the estimated 250 million preschool-age children now subclinically deficient. Adequate vitamin A status can be achieved through food-based strategies that provide naturally occurring preformed or provitamin A food sources and fortified food products, or vitamin A supplements. These programs often work well under controlled conditions but are less effective and sustainable when scaled up to regional or national levels. A deterrent to sustainability in low-income countries with vitamin A deficiency has been lack of long-range plans that consider the local context of the problem and how to integrate supplementation, fortification and/or dietary modification, through social marketing and education, within a development framework with time-bound and measurable achievement goals. Disease control programs—e.g., breast-feeding, immunization, and deworming—should be a part of the vitamin A-deficiency treatment and control programs because parasites contribute to inefficient utilization and conservation of the vitamin.

Successful elements of all intervention strategies include social marketing and education of targeted audiences, and for sustainability, community-based involvement in the process of designing, implementing, monitoring, and evaluating programs that affect the community. Even fortification programs that, on the surface, would appear to require only passive involvement, need an informed consumer to assure choice of fortified products when there are non-fortified, often lower-cost, alternatives. High-dose, disease-targeted supplement distribution and disease control programs favor implementation through the PHC-infrastructure, whereas the low-dose supplements frequently distributed lend themselves to private sector, community control. Community-based, low-dose programs, however, have not yet been broadly tried and evaluated in low-income countries. Fortification programs in the long term are the most cost-effective and sustainable, although not immediately feasible in some affected societies.

Successful country experiences in progressing toward elimination of VAD at a public health level of significance illustrate the importance of long-term, integrated program planning within a national, as well as human, development framework. Careful context-specific integrated program planning can achieve measurable results in as little as 5–10 years, or require longer periods, depending upon the resources and infrastructure available to support and sustain these efforts. Stable political and resource commitment and flexible resource management

for program support are critical to sustaining incremental progress toward elimination of vitamin A deficiency of public health significance.

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5

Prevention of Iodine Deficiency

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Iodine Deficiency Disorders

REQUIREMENTS FOR IODINE

The thyroid hormones, thyroxin and triiodothyronine (T4 and T3), contain four and three atoms of iodine, respectively (For a comprehensive review of this section, see Hetzel, 1989b). Triiodothyronine, formed by monodeiodination of thyroxin, is the effective hormone. Iodine must be obtained from the environment. It has no recognized role in mammalian biology other than as a component of the thyroid hormones, although there is some suspicion that iodine deficiency may be involved in fibrocystic disease of the breast. Normal development requires the thyroid hormones. They are synthesized and secreted solely by the thyroid gland and are largely circulated in the blood bound to thyroxin-binding globulin and less firmly to other circulating plasma proteins (Braverman and Utiger, 1996).

The absolute requirement for iodine is quite small (DeLange, 1994). Adult needs can be met by 100 to 150 micrograms daily, with perhaps another 50 micrograms daily in the event of pregnancy. Infants and children require less overall, but somewhat more per kilogram of body weight. The capacity of the thyroid to store iodine, the relatively long half-life of thyroid hormone in the blood, and the capacity of the thyroid system to adjust to fluctuating supplies of iodine ensure a constant supply of thyroid hormone to the organs and tissues of the body, although daily iodine intake fluctuates widely. The thyroid system is intrinsically stable.

The normal thyroid contains between 2 and 20 mg of iodine. About 70 percent is in the form of the amino acids mono- and diiodotyrosine, the precursor molecules of the thyroid hormones. They are in peptide linkage in the large storage iodoprotein, thyroglobulin (MW about 660,000). The hormones

are released through proteolysis under the stimulus of thyrotropin from the anterior pituitary.

Iodine is absorbed with high efficiency after ingestion. Most iodine containing substances are deiodinated in the gut and the resulting iodine absorbed. It is captured by the thyroid from the blood at a rate dependent on the history of supply. Most appear in the urine in inorganic form in amounts that largely reflect recent rates of ingestion. The daily excretion is the amount absorbed and that derived from hormone degradation, but not taken up by the thyroid. Under normal circumstances, the thyroid takes about 20 percent of the available iodine.

There are limits: too little iodine over too long a time leads to serious consequences, as described below. When too much is ingested, the thyroid may shut down; under certain circumstances, it becomes overactive.

CONSEQUENCES OF IODINE DEFICIENCY AND ITS CORRECTION

Goiter

The anatomical response to chronic iodine deficiency is enlargement of the thyroid gland. Initially there is hypertrophy of the thyroid epithelial cells. With fluctuating iodine supply, involuntary changes occur; the epithelial cells flatten, follicles fuse to form nodules, degenerative changes occur, cysts form, and calcifications are seen. The changes may be highly irregular from one site to another within the gland. Iodine-deficiency goiter may appear in preadolescence and nodules may form when the deficiency is severe, but there is usually a modest enlargement in the young that progresses over the years to multinodular goiter (Kopp et al., 1994; Parma et al., 1994; Taylor, 1953). It is customarily more evident in the female; regression usually occurs in the postadolescent male. When deficiency is severe, goiter rates may approach 100 percent, even in the young.

Goiter is usually harmless, if unattractive. Nevertheless, nodules may cause tracheal obstruction or impair the function of the laryngeal nerves. When surgery is required or elected, the risks of surgery in the local setting must be considered, and these may not be negligible. Malignant degeneration is a much debated issue; there is probably a slightly increased risk in endemic goiter (Riccabona, 1972).

Mental and Neuromotor Retardation

Neuromotor and cognitive impairments are the most important consequences of iodine deficiency. The endemic cretin is the classic example.

This outcome is seen when iodine deficiency is severe and of long duration; it is also likely that the mother has been severely iodine-deprived. The damage begins during the second trimester of pregnancy and is reversible if iodine is supplied, but the damage sustained after the end of the second trimester is permanent (DeLong et al., 1989). The neurological features are characteristic and distinct (DeLong, 1989). In addition to severe cognitive impairment, they may include hearing and speech deficits; a distinctive proximal neuromotor rigidity with sparing of the distal extremities; and, in some instances, cerebellar signs. Cretins are usually tractable and can often perform simple tasks; autonomic function seems undisturbed. DeLong has pointed out that head circumference is often reduced. The hearing impairment may arise both from middle-ear and central damage (Halpern, 1994).

Less extreme levels of iodine deficiency are responsible for lesser degrees of impairment, but the number of individuals affected is much greater than the population subject to the effects of severe deprivation. These changes extend from modest but detectable neurological changes to impaired learning capacity and performance in school or reduced capacity to handle formal tests of psychomotor function (Stanbury, 1994). A crucial question, and one that is difficult to answer, is how these changes within the community affect socioeconomic development. The consequences of moderate degrees of iodine deficiency for cognitive and motor performance have been examined in great detail (Stanbury, 1994). One of the earliest formal observations arose from the case of a village in rural, Andean Ecuador. Many residents were without physical deformity or other signs suggestive of cretinism, but it seemed quite obvious that they were mentally retarded (Dodge et al., 1969a,b). A meta-analysis of 18 studies of cognitive and neuromotor function (Bleichrodt et al., 1989) that covered a total of 2,214 individual subjects provided mean scores that were 13.5 IQ points lower in the iodine-deficient group than among the controls.

Reproductive Impairment

Rates of reproduction may continue to be high in iodine-deficient populations, but there is evidence that the rates are lower than in otherwise similar communities that are not deficient (McMichael et al., 1980; Pharaoh et al., 1971; Thilly et al., 1980). There are many possible reasons for this disparity. Fetal and pre- and postnatal survival are reduced by iodine deficiency (Connolly et al., 1979), as is motor performance during childhood (Connolly et al., 1979). Correction in one group of Chinese communities resulted in a doubling of the survival rate of neonates (G. R. DeLong, Division of Pediatric Neurology, Duke University Medical Center, personal communication).

Impaired Agricultural Productivity

Information on this point is scanty, but the question is an important one. DeLong (1989) has reported from China that there has been a remarkable increase in sheep survival and growth following introduction of iodine into the drinking water in an iodine-deficient region. The value of introducing iodine in the sheep industry of Australia and the cattle industry of the American Northwest has been reported, and iodine supplementation of feeds has been implemented. There is little evidence that iodine has any influence on plant growth. (Pandav and Mannar, 1996).

Economic Stagnation

While it seems intuitively obvious that iodine deficiency causes economic stagnation, it is difficult to produce unassailable supporting evidence. Socioeconomic conditions improved dramatically in a traditionally deprived and backward village in China, Jixian, after iodization of salt, but confounding variables leave doubts about the exclusive role of the fortification (Hetzel et al., 1987). Reduced energy, lowered learning capacity, and the burden of increased fetal and postnatal mortality must surely impede socioeconomic development (Dunn, 1994a; Hershman et al., 1986).

Physical Growth

It has been difficult to prove a relationship between physical growth and iodine nutrition alone because of the confounding variables of the other deficiencies that are usually present in iodine-deficient regions (Greene, 1973). Nevertheless, hypothyroidism (a consequence of iodine deficiency) clearly retards growth and development, and iodine-deficient individuals frequently are shorter than their iodine-sufficient peers.

CONSEQUENCES OF THE CORRECTION OF IODINE DEFICIENCY

Correction of iodine deficiency pays huge dividends in improved quality of life, elimination of cretinism and other lesser degrees of neuromotor and cognitive function, improved survival, and so on, but correction programs are not without some undesirable consequences (see following section on Costs and Benefits). Whenever thyroid nodules develop in the iodine-deficient gland and iodine is introduced—especially if introduction is poorly controlled and monitored—a fraction of the population will develop thyrotoxicosis. Because autonomy of function occurs in the iodine-deficient thyroid as a consequence of

mutational events, it is probable that the changes are irreversible without medical intervention. The magnitude of this problem is not known. Epidemics of thyrotoxicosis were reported when iodine was introduced into the diet in the United States, Tasmania (Stewart and Vidor, 1976), and a number of other countries, but the consequences have not been measured in their prevalence and long-term damage. The problem is age-old: how much harm can one accept in order to reap the many obvious benefits?

INTERACTION WITH OTHER MICRONUTRIENTS

Interactions of other micronutrients with iodine deficiency have not been defined with sufficient clarity, and further investigation is needed. Vitamin A deficiency may impair thyroid hormonogenesis by reducing retinol-binding protein, which is involved in glycosylation of the key protein thyroglobulin (Ingenbleek, 1983). It was observed that the presence of vitamin A deficiency appeared to worsen clinical features of iodine deficiency in Senegal (Ingenbleek, 1983). Selenium is a key component of a large number of enzymes, some of which, such as thyroxin deiodinase, are involved in thyroid function. Lack of selenium, a component of glutathione peroxidase, may contribute to the accumulation of peroxide in the gland, which is destructive and may contribute to the damaged gland observed in a study of the cretins of Zaire (Contempre et al., 1995). Uptake of iodine by the thyroid is an oxidative process, and energy is required for hormone synthesis and secretion. These processes require iron-containing catalysts, but the role of iron deficiency in thyroid function is not well defined. Iron is less well absorbed in the hypothyroid state, and subjects with hypothyroidism are frequently anemic (Ansell, 1991).

While not micronutrients in a restricted sense, other dietary components may contribute to the impact of iodine deficiency. One group, the thioglucosides, such as linamarin, found in cassava, yields thiocyanate on hydrolysis in the gut if improperly prepared, and the resulting thiocyanate competes with iodine for uptake of iodine by the thyroid. There are many other dietary and environmental substances that interfere with thyroid function that merit consideration (Gaitan, 1989).

EXTENT OF IODINE DEFICIENCY

Assessment Techniques*

Goiter Rates

This traditional technique continues to be useful as a preliminary screen or when more precise methods of assessment are not available. It has the limitation

* Hetzel, 1989b; UNICEF, 1994.

of observer variation, especially in classifying thyroids of smaller sizes by palpation. In recent years ultrasonography has permitted improved precision and definition of what is abnormal; it has also provided a graphic account of structure. The technique can be applied in field conditions with portable equipment, and subject turnover can be quite rapid and efficient.

A simplified classification for practical purposes is provided below in Box 5-1, adapted from a consensus statement by ICCIDD, WHO, and UNICEF (UNICEF, 1994).

Iodine deficiency may be strongly suspected if more than 5 percent of school-age children fall into grade 1 or 2.

Ultrasonography is rapidly becoming widely available for estimation of thyroid size and configuration. Several recent studies (e.g., DeLange et al., in press) have established mean and median values for normal thyroid volume in relation to age, gender, height, weight, and body surface for iodine-sufficient children. Thyroids greater than 2 standard deviations (SDs) from the mean for normals are classified as goiters. This method can be applied to as many as 200 children in a day. It has the advantage that it may disclose nodules that are missed in routine examination.

Urinary Iodine

Advances in methodology now permit rapid and accurate measurements of the iodine in urine. When done in samplings of appropriate size, these measures provide an excellent measure of the recent iodine nutrition of a community (UNICEF, 1991). The results are customarily expressed in ug/L; values below 50 are considered unacceptably low, and those above 100 are taken to signal sufficiency. Values below 25 ug/L indicate an urgent need for preventive action. Measurement of urinary iodine (UI) in representative samples from a population is presently the most convenient and reliable method to assess iodine nutritional status (Dunn et al., 1993a,b). Many studies confirm that iodine excretion rates correlate inversely with goiter size, and that when values are very low, the prevalence of neuromotor and cognitive impairment is high.

BOX 5.1 CLASSIFICATION OF GOITER

Grade 0: No palpable or visible goiter

Grade 1: Not visible with the neck in normal position. The mass moves upward when the subject swallows. Nodular alterations can occur even when the thyroid is not visibly enlarged.

Grade 2: A swelling in the neck that is visible when the neck is in a normal position and is consistent with an enlarged thyroid by palpation.

Measurements of UI (urinary iodine) serve as an excellent monitoring technique. Failure in programs of salt iodization can be detected, as well as the addition of too much iodine to the salt supply. Continuing spot monitoring of UI should be part of every prophylactic program, and occasional samples should be confirmed by an independent laboratory.

Measurements of TSH

The technology of TSH measurements has advanced rapidly and is becoming available for the assessment of iodine deficiency. There are easier and less expensive methods to detect iodine deficiency, but universal neonatal screening can provide a good ongoing indicator of iodine deficiency, and it can also monitor the adequacy of a continuing prophylactic program, provided the neonatal screening is *universal*. The samples should be collected by heel stick and spotted on paper for later analysis.

This technique is not yet available in most countries experiencing a significant iodine deficiency. It is also not applicable as an initial survey method unless there are sufficient births for sampling within the time frame of the survey, which is rarely the case. At the same time, surveys with larger population groups may disclose evidence of iodine deficiency if representative samples are available. The upper limit of normal in current assay methods is 5 to 6 uU/ml, and a significant number of results above this level suggests the presence of iodine deficiency. Introduction of high-sensitivity TSH assays has made it possible to determine the prevalence of iodine-induced thyrotoxicosis after the introduction of replacement iodine. Surveys of this kind could answer questions about the persistence and incidence of thyrotoxicosis or clinically inapparent thyrotoxicosis in regions with limited medical care. Values below 0.2 uU/ml raise concern about the presence of iodine-induced thyrotoxicosis.

The current disadvantage of TSH measurements as a survey instrument is cost. UI is far less expensive and more readily applicable in the field.

Thyroglobulin

The abnormal thyroid of iodine deficiency leaks thyroglobulin into the blood, and this can be measured routinely with commercially available kits. This may prove to be a more accurate and reliable method for the assessment of iodine deficiency than goiter surveys by palpation or TSH measurements (Benmiloud et al., 1994). The method is sensitive and can be performed on dried bloodspots (Missler et al., 1994). This measure is also nonspecific—other conditions raise serum Tg values just as they produce goiters, but such conditions are fairly uncommon in the general population. The available assays

vary in their normal range, and thus the technique and normative data must be specified when results are reported.

Persons with adequate intake of iodine have mean levels of serum thyroglobulin of 10 ng/ml, with an upper normal limit of 20 ng/ml. The method has the disadvantage of expense.

Iodine in Food and Water

Methods are available for field use to assess the presence or degree of iodine deficiency, but assays on food are difficult. Measurements of the iodine content of locally available water, while technically satisfactory, are at best a poor indicator of the level of iodine deficiency in the community because sources vary in less developed communities, there are seasonal fluctuations, and there is a poor correlation with the levels of iodine available from other sources.

Extent and Distribution of Iodine Deficiency

Iodine is sparsely distributed in the earth's surface. As a result, iodine deficiency disorders (IDDs) have been exceedingly common in most populations (Hetzel, 1989b; Hetzel and Pandav, 1996; Mannar, 1996). These disorders were highly prevalent in the United States prior to the introduction of iodine through iodized salt. In the past, IDDs were frequent in much of Western Europe, and a severe problem in most Latin American countries, throughout most of Africa, in the Middle East, in the Himalayan region and southward on the subcontinent, in China, and in Southeast Asia. Iodine deficiency is a current problem among the countries of the former Soviet Union. Fortunately, the efforts of the past decade have made signal advances in elimination of IDDs through universal salt iodization (USI).

WHO has estimated that over 1.5 billion persons worldwide reside in regions of environmental iodine deficiency (ID) and are at risk of IDDs. This may be a soft figure, but it suggests the importance of the problem for public health. Of those at risk, possibly half have clinically detectable thyroid abnormalities; of this group, probably one-fifth have health-significant impairments, and an unknown number have reduced intellectual function. Recognition of the baleful effects of iodine deficiency on the development of the nervous system has led to the recognition of ID (iodine deficiency) as the most common cause of preventable mental retardation in the world.

Economic Costs of Iodine Deficiency

Any attempt to assess the costs of iodine deficiency would be subject to tenuous assumptions and large-scale errors. Costs would be region-dependent:

for example, the costs of a case of cretinism in the rural highland Andes or Central Africa are not comparable to the costs in an industrial region. The costs of lost productivity, premature death, fetal losses, and reduced energy would require—at best—guesswork.

The costs of surgical procedures for goiter in Germany have been calculated, and they have been huge (Gutekunst, 1993). It has been said that only a few years ago, half the surgical procedures done in the major hospital in western Austria were performed to address goiter. Thyroidectomies were the mainstay of some of the busiest and most important clinics in the United States before the iodization of salt.

Calculating costs without comparing benefits would be a relatively pointless enterprise. When efforts have been made to do so, the ratio of benefits to costs has been enormous (Correa, 1980; Dunn, 1994a; Hershman et al., 1986). Prevention is thus a highly advantageous undertaking.

INDICATORS OF IODINE DEFICIENCY AND IMPACT OF PREVENTION

Identifying Target Populations

One may begin with the assumption that ID exists virtually everywhere, except where satisfactory prevention programs have been introduced or in the few regions of the world with ample iodine in the environment. What is a target population for an intervention program? Is it one with a borderline or moderately low mean daily intake of iodine, but no clinically evident IDDs, or only populations with positively identified IDDs? The former condition and grades of the latter will dictate the urgency of a program of fortification or supplementation.

Identification of a target group is partially dependent on formally designed surveys that employ one or more of the tools described above. The structure of surveys depends on local or regional conditions, geography, transport, and resources. Highly stylized epidemiological surveys run the risk of missing important pockets of IDDs; some exploration may be required to follow up dubious information or intuition.

Monitoring Intervention Programs and Their Impact

The key to success in prevention of IDD is longitudinal monitoring of both the supply of iodine and the impact of the prevention program on the targeted population. Too many programs have lapsed because of failed monitoring, with the subsequent reappearance of IDDs. Monitoring should be institutionalized on a continuing and stable basis. The iodine content of salt should be measured

from the factory or import portal, to the retailer, and on to the household. Swings in concentration should be investigated and corrected. Quite simple and reliable methods are now generally available to measure the iodine content of salt to assure that it is within satisfactory limits (Sullivan et al., 1994). Results should be confirmed by external control laboratories.

The impact of programs should be monitored by periodic assessment of the status of IDDs. Success is signaled by a decline in IDDs as indicated by one or more of the assessment techniques described above. Care is needed in interpreting the information gained through monitoring, For example, if the surveyed population is comprised of older subjects with long-standing goiter and the technique of assessment is goiter rate, little change may be observed.

The time frame for monitoring depends on what is being monitored. The iodine content of salt should be monitored on a daily basis at the factory or at the point of import and it should be frequently checked again at the store or point of sale, whereas little would be gained by measuring thyroid size more frequently than once each year. A national neonatal TSH screening program—if universally employed—would provide continuous monitoring of the frequency of IDDs.

The ideal framework for monitoring would include most or all of the following components. Monitoring must include appropriate and effective responses if deficiencies are detected:

- After an initial goiter survey by ultrasonography, zones of suspicion would be monitored annually.
- A neonatal TSH screening program that is *universally* applied is needed.
- The iodine content of salt is monitored daily at the site of production or point of import.
- Spot monitoring of table salt is done at the retailer and at the consumer's table.
- Measurements are taken of UI. Initial measurements are made in statistically valid samples; measurements are done occasionally after the program of iodine distribution has begun.
- Measurements are made of plasma thyroglobulin in statistically valid samples of serum.

PREVENTION AND CORRECTION

Fortification

Salt*

Fortification of salt has a unique advantage among the micronutrient supplements—it requires no change in dietary habits, because everyone uses salt

* Fernandez, 1990; Mannar, 1996.

(Mannar, 1996). The one disadvantage it shares with any other program of micronutrient fortification is that the improved product costs slightly more than the original. This must be countered, either through subsidy by donor organizations or by intensive social marketing that makes the iodized salt more desirable and worth the additional cost. The experience is that cost has rarely been a major stumbling block. Importation of noniodized salt across borders has occasionally been a problem, especially when the product has been labeled as iodized but actually contains no iodine. Small traders or local producers of salt near salt deposits have been a problem in rural Bolivia, Ecuador, and Argentina, for example. Demand for the iodized product has been created by professional social marketing techniques, as in Ecuador. Mass media campaigns that employed posters, press, pamphlet distribution, and radio were used in all regions.

The goal in the prevention of IDDs is universal salt iodization (USI). Programs must take into account possible losses between point of manufacture or import and the consumer's table. Losses may vary among the forms of iodine used (iodide vs. iodate), heat, purity, humidity, packaging, shelf time, and losses in cooking. Programs should also be designed around salt consumption patterns in order to make the maximum effort to ensure an intake of iodine within the desired range. A mean consumption of 15 grams or more daily has been observed in some communities; in others as little as 2 grams have been consumed. Salt may be iodized in several ways, including dry mixing, drip, or spray techniques. Generally the iodine is sprayed or drip-fed on the salt as it flows down a mixing-screw conveyer; if the salt is finely ground, the iodine may be added dry (Dunn, 1995; Holman and McCartney, 1960). The long-term costs of producing iodized salt to supply the needs of an individual amounts to only three or four cents yearly. Unfortunately, in some instances a high, unwarranted premium is added to the cost of the salt to the consumer. Iodine is available principally from Chile and Japan.

Difficulties arise in implementing programs when the salt industry is widely dispersed among a large number of small producers. Ensuring distribution of iodate to all parties for local production is difficult, and compliance is a problem. In Thailand, small, electrically powered rotating drums for mixing iodate into the salt are manufactured and are being widely distributed to remote areas to address this problem.

The increasing use of plastic bagging has reduced iodine losses between manufacture and consumer, as has the sale of smaller packaging to effect more rapid turnover of the product.

A customary level of fortification is in the range of 25–50 mg of iodine per kg of salt. This level will require variation to accommodate local conditions. The cost—considering all factors of plant operation, cost of the iodate, and control—should add little to the cost to the consumer and is a trivial increment, considering the low cost of bulk salt. When the salt is imported it must be reprocessed

at the portal of entry, or the supplier must be convinced to cooperate and ship only a properly iodated product.

A final determination of cost must include expenses of the iodine, processing costs (including labor and supervision), packing (including polyethylene lining of the containers), shipping, administration (including monitoring), and plant amortization. One estimate has placed the total cost, in addition to that of the basic salt, at US$0.02 to US$0.06 per person yearly. This represents somewhere between 2 and 20 percent of the retail price of the product.

Experience has shown that most manufacturers or suppliers of salt are quite willing to cooperate in iodinating their salt, once the importance of salt fortification has been explained. In some instances international agencies, particularly UNICEF, have been instrumental in introducing USI (universal salt iodization) and have assisted producers by supplying the machinery required for the iodization process.

An outstanding need in the salt iodization process is maintenance of the level of added iodine within safe and effective limits. This means, at the very least, that the concentration of the commercial product must be measured at frequent intervals. Fortunately, the technique required for this measurement is reasonably accurate.

Iodinated Bread

Three programs—in the Netherlands, Russia, and Tasmania—have used bread as a vehicle for the distribution of iodine. Both the Dutch and the Australian programs were dropped for logistical reasons, because of an attendant rise in iodine-induced thyrotoxicosis, or because iodine became available from other sources. The Russian program is too recent to judge, but it appears promising in communities where bread is centrally prepared and iodized salt is unavailable.

Iodinated Water

Water has been successfully used as a vehicle for the prevention of IDDs. A silastic cylinder containing iodine has been used in bore holes in several African countries to achieve some success in raising community iodine intake, but the many associated difficulties have prevented its widespread use (Fisch et al., 1993). In selected rural regions of Thailand and Indonesia, iodine is added intermittently to cisterns that store water for drinking and cooking (Suwanik et al., 1989). The current program of USI in Thailand will doubtless eliminate use of this method in the near future. Iodine has been introduced into city water supplies in Sicily with a bypass through an iodine-containing canister. Reduction in IDDs was reported, but the method fell into disuse because of mechanical, legal, and monitoring problems.

An ambitious program to introduce iodine into irrigation water in the desert areas of western China (by DeLong and colleagues) has been hugely successful in increasing yields in sheep farming and in reducing infant death rates (G. R. DeLong, Division of Pediatric Neurology, Duke University Medical Center, 1997, personal communication).

Supplementation

Drops and Tablets of Iodine

The original study that proved iodine prevents goiter used sodium iodide, which was given to schoolchildren twice yearly (Marine and Kimball, 1921). Drops of Lugol's solution have also been used in schoolrooms. Tablets of salts of iodine, sometimes disguised with chocolate, have been dispensed intermittently. Recently there has been renewed interest in intermittent dosage in classrooms using tablets or drops containing iodine.

Iodinated Oil

Iodinated poppy seed oil has been widely and successfully used in the prevention of IDDs since its introduction in the late 1950s in New Guinea (Fierro-Benitez et al., 1969; Hetzel et al., 1980). Other unsaturated oils have also been used. Needs may be met for a year or more by a single dose, depending on its size and route of administration. These mixtures have been used both intramuscularly and orally in doses varying from .2 ml to several ml. Most programs have used either 1 or 2 ml in older children and adults, but success has been achieved with smaller doses (Benmiloud et al., 1994). Side effects have been virtually nonexistent, except for occasional instances of induced thyrotoxicosis. The technique is more expensive than USI. Depending on the logistical and administrative costs added to the cost of the iodinated oil, the cost totals approximately US$0.10 to $0.50 per person annually. A major expense will be determined by the costs of the team, which is often posted to remote regions. Iodinated oil has been accepted well by target groups. It is currently reserved for communities where it is unlikely that USI will be introduced within the foreseeable future (and such areas are disappearing) and areas where the need is urgent and USI is unlikely to reach the target population immediately.

Irrigation water has been successfully iodinated in western China (Cao et al., 1994). The water is derived from glacial streams, and never reaches the sea. All farms and households in the region subsisted on this water. Potassium iodide in 5 percent solution was slowly dripped into the water from tanks at a rate that provided approximately 10 to 80 µG iodide per liter for several weeks each season. There followed a sharp rise in iodine excretions among the population and

a sustained rise in iodide in the soil. Improvements were noted in survival and weight gain among domestic animals, and growth of children also improved.

Summary Statement on Fortification and Supplementation

No one questions the priority of USI in the world program for the elimination of iodine deficiency and its disorders. The use of iodinated oil, iodinated water, iodinated bread, and tablets and drops are all reserved for special circumstances until IDDs are eliminated as a health problem. Of the alternative methods, iodinated oil has proved to be the most successful, but it requires a skilled team, availability of disposable syringes and needles, and carries an attendant risk of infection. Nevertheless, iodinated oil has a well-defined role in the international campaign against IDDs. Other modalities are limited to special circumstances. With support as needed from the international health agencies, USI should continue to move rapidly forward, with only occasional and limited requirements for other methods of prevention.

NATIONAL PROGRAMS: SOME EXAMPLES OF SUCCESS AND FAILURE

Ecuador

Context

There is evidence of the presence of endemic goiter in Andean Ecuador reaching back to pre-Columbian times. Goiter was occasionally mentioned over the years, and in 1957–1958, a national survey disclosed a remarkably high prevalence of goiter and cretinism. At about this time, Professor Rodrigo Fierro-Benitez began an intensive study of the prevalence and pathophysiology of goiter in several remote villages north of Quito, and in 1966 he began a controlled trial of the administration of iodinated oil. Although there was legislation prescribing iodization of salt, compliance was spotty and intermittent, depending on the interest of the government and the Ministry of Public Health.

In 1984 a joint enterprise between the government and the foreign assistance program of the government of Belgium was inaugurated, and experts from Ecuador have worked closely with their Belgian counterparts since that time. A central office under the guidance of an Ecuadorian expert was established, and a strategy was developed that proved to be efficient in the control of the deficiency. Small and well-trained teams were placed in every affected province to intensify education and communication activities and to begin a surveillance system that is still in place. A system for data collation was established. General education, using both Spanish and Quechua, regarding salt iodization was promoted through individual schools, radio spot commercials, slide shows, lectures,

and the press, and the cooperation of the salt industry was secured. Meanwhile, research activities under Dr. Fierro's direction continued to provide information on the effectiveness of the iodinated oil program. He was also a key figure in the continuing encouragement of the Ministry of Public Health to assist in the program. Both UNICEF and WHO, together with the Belgian contingent, have been important forces in sustaining interest and activity in the program.

Results

Once a country with an extraordinary high prevalence rate of IDDs, Ecuador has now achieved virtual elimination of these disorders. The program with iodinated oil was initially extended to many villages in the highlands, with excellent results. Iodized salt has now replaced iodinated oil, and it reaches virtually all consumers. There has been only an occasional intrusion of contraband uniodized salt, from the north. Surveillance continues and appears to be established as a permanent operation, with the central government assuming increasing responsibility. A recent survey by ultrasonography in a previously severely affected area disclosed the absence of goiter in all persons who had received prophylactic iodine, except for older individuals, some of whom retained firm nodules that were established before the programs began.

This successful program illustrates the importance of persistent efforts by dedicated medical scientists, working in concert with the national health sector and bilateral and multilateral agencies. This long-term cooperative venture lends optimism to the prospect of continuing eradication of IDDs from the country.

Nigeria

Context

Nigeria has not been identified as a site of severe IDDs except in a few isolated regions, but a modest prevalence in at least eight states has long been recognized, and approximately 25 million people live in iodine-deficient regions. Iodization of salt has been recommended for at least 15 years, but has rarely been implemented. In the late 1980s an expert committee recommended formation of a national committee to review the problem, and mandatory iodization of salt has been recommended. A key to the strategy was a shift from dependence on the government to active involvement of the private sector. All of Nigeria's salt is imported, and there are only three major salt companies. Of these, the largest, Union Dicon Salt, processes 500,000 metric tons of the 630,000 metric tons utilized annually in the country. The company carefully monitors the iodine content of the salt produced. By 1995, 97 percent of the salt produced for human use was iodized (Asquo, 1995; Dunn, 1996b). The company has also been active in the promotion of iodized salt through local advertising efforts. In the

1980s a team from Japan made a series of surveys and investigations in the center of the country and forwarded a set of recommendations to the government, but these have not yet been implemented.

Results

It is too early to judge the effectiveness of the national committee or its longevity. Political turbulence has hindered progress toward a well-established national program, and imported salt from neighboring countries has also made control difficult. It thus appears that while there are committed and active individuals and organizations in Nigeria, they find significant impediments to a needed national program. Not the least of these is a failure to recognize IDDs as a significant problem. Nevertheless, the experience of Union Dicon Salt illustrates the contribution that a socially responsible industry can make in the fight against IDDs. Cultivation of such companies can be important.

Bolivia

Context

Landlocked, largely mountainous Bolivia has been known for goiter since colonial times. In 1981, a survey disclosed a goiter prevalence rate of 68.1 percent. A national program against goiter began with the formation of PRONALCOBO, a government agency, in the early 1980s. A crash program was initiated in 1988, and a large campaign using iodized oil reached about 1.4 million persons and continued until USI became institutionalized. A few highly isolated communities remain where iodinated oil is still necessary. The project was initiated with the help of funds provided by the Italian government. Implementation has relied on the country's well-developed regional health care system, and the project has been administered through each of the nine sanitary units. Nonprofessional community health workers throughout the country had the responsibility for the actual delivery of the oil, and they were aided by community organizations such as schools, political groups, and religious organizations. In each instance, records of individual subjects were kept.

Results

Goiter prevalence fell from 65.3 percent in 1983 to 23.6 percent in 1989, and it has continued to fall. Median urinary iodine levels are well above 100 mg/L. Salt, which is available from abundant sources in the country, is iodized, packaged, and marked within the country (Dunn, 1996a; Havron, 1988). The major challenge now is sustaining the achievement. Past experience in Latin

America and elsewhere predicts that iodine deficiency will reemerge unless a sound monitoring system is in place. This success story points to the value of the combined, persistent efforts of a hardworking organization; international agencies and experts; and, most notably, national experts devoted to elimination of IDDs, such as Dr. Antonio Pardo. Together, these forces have created a program that gives every indication of continuing to succeed in a country where one would have every reason to believe that IDDs would return without prophylaxis.

Guatemala

Context

Following the establishment of the Institute of Nutrition of Central America and Panama (INCAP) in 1949, several surveys were completed by the new institute that pointed out the high prevalence of goiter, although the technique used recognized only highly evident thyroid enlargement. The mean was 38 percent for the country and 55–59 percent in four departments (Dunn, 1991). By the early 1950s, INCAP had established the availability of iodine from potassium iodate, which proved to be stable in the crude, moist salt sold in the country, even in the tropical lowlands. INCAP persuaded the government to require the iodization of all salt for human consumption, and this began in 1956 at a level of 10 to 20 mg/kg. Compliance was monitored by the Department of Health. Guatemala went through a particularly turbulent political period in the 1980s, and the leadership of INCAP was decimated by the terrorist kidnapping of the director and administrator and by threats that caused most expatriate professionals to leave. In the early 1990s goiter had reappeared, and the salt was no longer being iodized. In 1995 the government restored salt iodization, but no new national survey has been available.

Results

The failure of the program in Guatemala points to the disastrous results that follow failure of government support and when no established agency has taken the responsibility to be continuously mindful of the latent risks of iodine deficiency. In this instance, the powerful INCAP organization was weakened. The federal agencies needed constant reminders of the potential threat of IDDs, even when the problem seemed to have disappeared. Political instability compounded the difficulties.

United States

Context

After the demonstration by Marine and Kimball in the American Midwest that iodine prevents goiter, there was a huge wave of enthusiasm for resolution of this widespread and serious problem (Marine, 1923; Markel, 1987). This enthusiasm was expressed through many articles in medical journals and the lay press, voluminous advertising, and the cooperation of the salt industry. At about the same time there was testimony to the effect that salt iodization could be dangerous to subjects with nodular goiter, and a number of articles appeared that condemned the use of iodized salt. Salt iodization never became an issue for the federal government, and there was no legislation in the area, but the beneficial effects of iodization were quickly appreciated. In more recent times iodine has been widely used in a variety of ways, including its inclusion as a water purifying agent, in many medications, and in the dairy industry. The result has been that the mean daily intake of iodine has risen well above minimum daily needs, and there is a consensus that the United States has no further need for iodization of salt.

Results

IDDs have vanished from the United States. Although iodized salt can be obtained in markets throughout the country, noniodized salt can be purchased as well, and there is no further pressure to use the iodized product. Thyroidectomy, once performed many times daily in the major medical clinics of the country, is necessary only when nodular goiter arises from a cause other than iodine deficiency. There are other indications of the absence of IDDs as well. The lesson to be learned from the experience of the United States is that in an advanced economy with a homogeneous food supply, especially if iodine is widely used in the dairy industry, there is a strong probability that iodine needs will be largely met without fortification. Nevertheless, iodine deficiency of mild degrees continues in some advanced countries of Europe, and occasional surveillance is still necessary.

Bhutan

Context

This country belongs to the Himalayan chain that has always been known for a high prevalence of IDDs. It fiercely maintained its independence and isolation until recently. Surveys in the late 1980s disclosed an overall goiter prevalence of about 60 percent, with rates as high as 85 percent in some regions

(Dunn, 1994b). Cretinism has been common. In the western region, UI was less than 25 ug/gm creatinine in over 50 percent of those surveyed, and some villages harbored a 10 percent cretin population, with no estimate of the number of "subcretins." All salt is imported through the town of Phuntsholing on the Indian border. The import and distribution of salt is managed by the Food Corporation of Bhutan, a government operation. A plant for salt iodization was established at the portal of entry in 1985, and it has slowly begun to iodize all salt at a level of 60 mg I/kg. Administration of iodinated oil was initiated, and more than 50,000 injections were given along the border with India, where there was some infiltration of noniodized salt, but this program is giving way as tighter control of salt iodization is realized.

Results

Tight control of iodization of all salt in the kingdom appears to have been achieved. This has resulted in the finding of adequate amounts of iodine in samples of urine collected in the course of surveys, and the salt seems to be adequately, but not excessively, iodized. The median urinary iodine levels were approximately 250 mg/L in the follow-up in 1992. The salt iodization system occasionally breaks down, which creates the need for better control at the entry point. Because of distance, salt may not be purchased frequently by the householder, and monitoring at that level needs attention. There is also a need for increased education of the general public and the field workers. A serious risk is that as foreign assistance for the operation is phased out, the government may not support the continued operation of the several facets of the county's control program. The lesson to be drawn from the Bhutan program is that careful initial planning, which must include planning for the long term, is needed. It is also evident that planning must involve several sectors of the government, including those responsible for health, economic affairs, and education. Planning must also include provision for monitoring both the salt supply and the population; ideally, a system for universal neonatal screening would be in place as well.

Zimbabwe

Context

Landlocked Zimbabwe has been known to have endemic goiter for at least 35 years, with goiter rates in some regions as high as 73 percent. With independence in 1980, a Department of National Nutrition was formed within the Ministry of Health and was charged with oversight in the area of micronutrients. In one region, the Chinamora District, levels of iodine in the urine were between 25 and 50 ug/gm creatinine. Planning to address this deficiency included a program to administer iodinated oil in the severely IDD-endemic areas and to institute

USI by the year 1990. An impediment to progress is the need to import all salt, from South Africa for the most part. The import of iodized salt slowly began to build up in about 1992. In late 1994, the mean concentration of iodine in salt collected nationwide was 29 mg/kg, and 81 percent of samples had at least 10 mg/kg.

Results

By late 1994 or early 1995, physicians began to report an increased rate of thyrotoxicosis, and in 1995 a survey of attendance at the teaching hospital in Harare disclosed a near-tripling of such patients (Todd et al., 1995). These cases were primarily, but not exclusively, among the elderly with nodular goiters. Fourteen deaths were recorded. These occurrences led to considerable international concern, and much tighter controls were imposed on the level of iodization of salt coming into the country. The lesson of the Zimbabwe experience is that whenever iodine supplementation or fortification is introduced into an iodine-deficient region, there will almost surely be a small number of subjects, especially those with nodular goiter of long standing, who develop thyrotoxicosis, and this occurrence must be anticipated. It is also evident that tight monitoring of the iodine content of salt—from producer to consumer—is needed, and the possible occurrence of iodine-induced thyrotoxicosis requires vigilance.

STRUCTURE OF PREVENTIVE PROGRAMS

The guidelines that follow are generally those recommended by the International Council for the Control of Iodine Deficiency Disorders (ICCIDD; Dunn and van der Haar, 1990). The prevention of ID is being rapidly subsumed by governments through their health ministries as USI is adopted. Initial programs were often begun by private voluntary organizations such as the ICCIDD, in close collaboration with USAID and WHO, or by the Belgian, Canadian, or Swedish foreign assistance organizations. Research into the pathophysiology or extent of IDDs sometimes served as the stimulus needed to take action. With the selection of IDDs as a priority concern by UNICEF and other international development assistance organizations, elimination of IDDs has become a priority goal of many developing countries, and the number is growing. Political disorganization, as currently seen in Central Africa, has not helped efforts toward this goal.

What is required for long-term success is the creation of a reasonably well-supported and stable commission or equivalent organization that is charged with advising the authorities to ensure continuing supervision of the program and adequate monitoring of the state of iodine nutrition in each individual country. Such commissions require support and continuity. They need to work closely

with the international agencies such as UNICEF, ICCIDD, and WHO. The commission or its advisees must run, or have ready access to, a laboratory equipped to perform the needed assays.

Assessment

It should be the responsibility of the IDD commission or its equivalent to carry out the periodic assessments described above, including regular monitoring of iodized salt and its effects. In addition, there should be periodic assessments of IDD status by an external, independent team working with the local commission. Results of these external reviews should be communicated to the respective governments for action.

Salt Industry

The salt industry should be involved in ID control from the beginning. In general, the leaders of the industry have been cooperative. Difficulties arise when the industry is badly fragmented into multiple, small producers. When salt is overly or inadequately iodized, this must be detected and corrected. The international assistance agencies have supplied manufacturers with the equipment to fortify salt in many instances.

Education

Education concerning ID is needed at several levels. Programs must be designed to inform the responsible governmental officials, including those in the health ministries; health care providers; the salt manufacturers and distributors; and the general population. A number of video productions have featured IDDs and have been distributed to appropriate audiences in many countries. Similarly, slide shows, flip charts, and radio spots have illustrated IDDs and the need for iodine. Country and regional conferences throughout the world have involved significant persons from countries where IDDs have been a problem in the past decade. An international IDD day, promoted by UNICEF and ICCIDD, has been an educational instrument.

Legal Approaches

Several countries, especially in Latin America, have enacted legislation requiring iodization of salt. In a few instances this has been useful, but in others the law has been ignored. It is clearly helpful to have this legislation on the

books. Care is needed in drafting legislation to ensure that requirements are not too rigid and can be adapted to local or regional conditions.

Why has legislation failed to be effective or been ignored? To the casual observer, IDDs do not appear to be a pressing problem in need of priority attention. Legislation has failed because the responsible health officials have not advocated enforcement of the legislation enacted, because funds have not been appropriated, or because other health problems have been more pressing. There have been occasions when the salt industry has not been cooperative or the execution of legislation has not seemed practicable because of the dispersed nature of the salt industry and the difficulty of assuring compliance. There have also been instances when misinformation has led the medical profession to oppose salt iodization.

The enthusiasm for IDD control that followed the 1990 UNICEF Summit Declaration has fostered a rash of legislation around the world. One fears that in some instances this will not be followed by sustained action. The solution will often be found in continuing attention to the problem of IDDs by individuals or small groups, especially when motivated by scientific or humanitarian groups outside the mainstream of government.

Having a law on the books that mandates iodization of salt is only a first step. The law must make provision for enforcement, which means the creation of machinery to inspect, monitor, and report. These functions all require a line item in the country's budget, and such expenditures may meet with resistance. The only solution appears to be the continuation of pressure and advocacy by interested persons until salt iodization is thoroughly imbedded in the economic culture of the country.

IMPEDIMENTS TO IDD CONTROL

Problems occur in policy, program structure, technology, and financial support for IDD control. Some of these are discussed below. Many publications and country reviews provide more details (for example, Dunn, 1996a,b,c; Dunn and van der Haar, 1990; Hetzel, 1989a; Pandav, 1994) of the difficulties encountered.

In the Domain of Policy

Inadequate Political and Popular Support

Hammering away at advocacy through a range of techniques should help create the needed support. For an IDD control project to work, it must be accepted by the government, including the health sector, and by the population at large. When salt iodization began in the United States, there was intense backing

by the popular press, organized medicine, and the salt industry. The federal government was not involved. Iodization took place largely through the advocacy of individuals who recognized the problem, wrote papers, gave talks, and educated the salt industry. This remarkable success story has been told only infrequently (Marine, 1923; Markel, 1987) and needs more extensive review.

Inadequate Involvement of the Salt Industry in Achieving Local or Universal Iodization of Salt

As noted elsewhere, salt manufacturers have generally proved to be cooperative in iodizing their product. The salt producers must be approached, informed, and encouraged. Means have to be secured to see that they are properly compensated for the additional cost of iodizing the salt. With the approaching universal iodization of all salt, it becomes necessary for the manufacturers involved in the international salt trade to join in the campaign.

Insufficient Education

The importance of IDDs and their correction should be made clear at all levels, including the government, the medical establishment, schools, and prenatal clinics and should be publicized through all available media.

Insufficient Monitoring

This major issue is discussed in the sections on Consequences of the Correction of Iodine Deficiency, and Monitoring Intervention Programs and Their Impacts. Proper and continuing monitoring is basic to achieving elimination of IDDs.

Complacency

Satisfaction with the status quo, forgetfulness, political instability, diversion of scarce financial resources, and intra- and interagency and governmental rivalries and feuding can all lead to sidetracking of IDD control programs and have done so in the past. IDD control must be embedded in the political structure, where it cannot be ignored.

In the Domain of Programs

The following impediments can damage efforts toward IDD control:

- Unreliable or inadequate field data, including assessment
- Insufficient monitoring
- Insufficient training of field workers
- Inadequate laboratory support
- Insufficient moral and financial support of organizations attacking the problems.

In the Domain of Research

The following is a partial list of the issues of importance to the implementation and success of programs for IDD control that require further research and clarification.

- Frequency, time course, and patterns of autonomy accompanying chronic iodine deficiency; reversibility; clinical impact over time, particularly after iodine replacement; dose effects. The problem of development of autonomy in the iodine-deficient thyroid is central to understanding the origin of IDDs. This issue is currently under active investigation and is closely allied to nodule formation and thyroid cancer. The question is yielding to the approaches of molecular biology.
- The effects and value of postnatal iodine replacement on growth and performance attributable to direct tissue effects (brain and somatic development irreversible) in comparison with effects mediated through reduced thyroid function (reversible). Some of the damage observed in the iodine-deprived individual is derived from irreversible disorders in the evolving nervous system, while other deficits are reversible and derive from postnatally limited hormone. There may not be a sharp dividing line between these two sources.
- Effects of prophylactic programs on social and economic development and performance and on agronomy. These effects are difficult to quantify and attribute because of the complexity of the factors that affect development. Nevertheless, there is emerging evidence of beneficial effects on the economy, such as sheep survival in China, where iodine has been added to the drinking water.
- Development of better and more easily and accurately applied monitoring tools, such as urine iodine measurements and Tg and TSH assays. An expensive, accurate, and easily applied TSH method for field application would be enormously useful and is possible with emerging technology.
- Mutations in the evolution of hyperplasia in the thyroid into nodules.
- Field research using kinase-interacting phosphatase (KAP) surveys to enhance implementation of prophylactic programs or determine why they are less than successful.
- Long-term outcome of the children of mothers with multinodular iodine-deficient goiters who received iodinated oil during pregnancy.

- Cost/benefit analyses are needed under a variety of economic and social conditions. These could have practical value in advocacy, but such research has rarely been attempted.

In the Domain of Financial Support

Conditions

If ID and IDDs are to be minimized, it is the obligation of the international agencies (WHO, UNICEF, Swedish International Development Authority-SIDA [Sweden], Canadian International Development Authority-CIDA [Canada], USAID, the World Bank, UNDP, and foreign assistance programs of other developed countries) and the committed private voluntary organizations (PVOs) to assure that the requisite funding is secured and distributed responsibly. It is the belief of this author that realistic support must be provided for program and project execution, as well as for the required administrative costs. The individual countries also bear responsibility for support insofar as their economies and priorities permit.

Costs and Benefits

Only limited analyses have been made on the costs and benefits of IDD preventive programs, and much more attention is needed. Those that have been made are strongly in favor of prophylaxis. Further research is needed in this area.

Assessment. The costs of assessment will depend on the magnitude of the enterprise, the tools chosen, the terrain, the personnel, and the detail employed and desired. If one limits assessment to goiter size, the expense may be minimal, but the information obtained will also be limited. If one chooses a full-scale country evaluation of all aspects of IDD using sophisticated indicators, the costs will be substantial, but again, their magnitude will depend largely on local conditions, both political and practical.

The benefits of assessment that leads to interventions that eliminate IDDs are enormous, and far below the costs of IDDs or any control program. This estimate is largely intuitive. Any formal cost/benefit analysis should take into account that the benefits must be measured against the cost of IDDs, as well as the costs of a prevention program.

Programs. These costs depend on many factors, including size, intervention chosen (iodinated oil or iodized salt), level of monitoring, and the infrastructure available and its commitment and reliability. While the benefits to human (and animal) health are scarcely calculable, any cost/benefit analysis must take into account the costs of IDDs. The costs of a modest, or even severe,

mental deficiency in an agriculturally primitive society would be quite different from the costs of the same abnormality in the industrial world, and the ratio might be adjusted downward accordingly.

Value of Benefits. Several attempts have been made to quantify the benefits of IDD prophylaxis. These are subject to many assumptions, but the benefits clearly outweigh the costs by a substantial value. In India, Pandav (Pandav, 1994) found a benefit—cost ratio of 3. Correa (Correa, 1980) has estimated the value of improvements in the intelligence quotient brought about by iodization and elimination of cretinism with the gain in income, and found that iodization was more valuable than a number of other interventions, such as education, infant nutrition, and physical capital. Elimination of cretinism, improvement in general intelligence and neuromotor function, and an enhanced energy level are the dividends of the elimination of iodine deficiency.

ACTION PLANS FOR THE INTERNATIONAL AGENCIES

Independent Evaluation

Evaluation of the current status of ID, IDDs, and the structure of country programs has been made in a few countries by independent external teams. For permission, credibility, and future corrections, these evaluations must be requested by the respective governments. If no ID commission is operational, creation of such a body can be strongly recommended by the external team. External evaluation also assures objectivity. The external team must have access to suspect regions and must be permitted to obtain independent data. Its report should go to the responsible government agency. ICCIDD (International Council for the Control of Iodine Deficiency Disorders) has proposed guidelines for assessing progress toward the sustainable elimination of ID (see Appendix).

Strengthening Monitoring

Independent evaluation will necessarily take time. Meanwhile, monitoring is essential and urgent. This will continue to be a high priority for agencies involved in ID and IDD control, such as ICCIDD. Efforts are being made to improve methods for measuring iodine in salt and in urine. Failure to monitor the iodine content of salt could undermine the whole structure of IDD preventive programs by allowing wide variations in iodine content to continue uncorrected (Pandav, 1994).

Strengthening the Role of Regional and Country Program Directors

The commitment and participation of groups that have a network of regional coordinators and country members involved in micronutrient nutrition, such as ICCIDD, need to be enhanced. This requires enthusiastic and dedicated leadership in addition to fiscal resources.

Enhancing Cooperative Efforts among Agencies

There are instances where interagency rivalries have paralyzed progress toward elimination of IDDs. But there are also examples of agencies that have begun to work together because of their common objective of eliminating ID. There is plenty for everyone to do.

Pursuing Relevant Research

Needed research includes basic inquiries into the nature of IDDs, the impact of prophylactic programs on the health of differing segments of a targeted society, and applied research directed toward the improvement of programs. Research costs money, and the international agencies must recognize their obligation to support acquisition of new knowledge. (Examples appear elsewhere in these paragraphs.)

Extension of a Micronutrient Database

A database in iodine nutrition has been established by ICCIDD with USAID support. It can be readily accessed on ICCIDD's homepage (http:avery.med.virginia.edu/~jtd/iccidd/home.html), and contains country-based information on ID and IDDs and information regarding current and recent publications. Hundreds of papers appear each year that cover problems related to iodine deficiency, and many appear in journals that are not immediately available to all those in the field. Also, many of the publications derive from regional meetings or appear in agency publications that do not find their way into libraries. These elusive articles can be accessed with increasing ease through an extended database. Comparable information about iron and vitamin A could be added to this base.

Extending and Expanding Communications

E-mail is widely available to members of the ID and IDD community and is extensively used. ICCIDD has a page on the Worldwide Web, and it is linking with other databases, including those of Micronutrient Initiatives (which already

has a database on iron and vitamin A), the Salt Institute, and the Latin American Thyroid Association. Others are being developed.

Extending Advocacy

Advocacy must be expanded by exposing government officials, health professionals, and the general public to the IDD message through formal and informal pathways. Regional representatives should develop and exploit contacts with the appropriate persons in government and industry to promote advocacy.

Closing Gaps in Knowledge of the Extent of ID and IDDs

The ID map of the world needs to be completed. With the current rapid progress in the campaigns against IDDs, the IDD and the USI maps require frequent updating through information supplied by ICCIDD regional representatives and the other international agencies, such as WHO and UNICEF.

Conferences and Workshops at the Country, Regional, and International Levels

Conferences and workshops have proved invaluable in sustaining enthusiasm, consolidating knowledge, and identifying needs and opportunities. They require organizational effort and financial support. The former has come from ICCIDD or its regional representatives, but the financial support has come, and will continue to come, from the international agencies; private foundations, such as the Thrasher Research Foundation and Kiwanis; and industry, such as Merck Darmstadt and segments of the salt industry.

Resource Development

Funding for ID, IDD action plans, and the organizations involved is currently grossly inadequate for the task of sustained correction. The bilateral and multilateral international agencies and nongovernmental organizations (NGOs) must constantly be reminded of their commitment and obligations to the correction of iodine deficiency.

Dedicated Team Approach

A useful approach to IDD elimination is offered by a team comprised of persons of diverse professional and geographical backgrounds that is organized

to work as a unit in correcting micronutrient deficiencies. The ICCIDD has been one such group since its formation in 1985. It has been a resource for the development and guidance of programs; advocacy through conferences, publications, and personal contacts; aggregating a large constituency; and research regarding the varied aspects of IDDs. Such a group can only be successful if it is comprised of professionals who are dedicated to the mission. Examples of such individuals, and their years of involvement in IDD elimination, would include Fierro-Benitez in Ecuador (35 years), Pretell in Peru (30 years), Pandav in India (20 years), Lantum in Cameroon (15 years), Kavishe in Tanzania (10 years), and others.

SUMMARY

In summary, the following points are cited.

1. The thyroid hormones are essential for normal development. Iodine, an integral component of the thyroid hormones, has no other function, although a role has been suggested, but not proven, in fibrocystic disease of the breast and stomach cancer. Iodine is scarce in most countries, and when insufficient, results in the iodine deficiency disorders (IDD). Prominent among these is retarded neuromotor and cognitive development of varying degrees of severity, depending upon the degree of the iodine deficiency.
2. Although much progress has been made in the past decade in the control of iodine deficiency in many countries around the world, the problem of the disorders deriving from iodine deficiency continues to exist.
3. Iodine deficiency and IDDs have largely but not entirely disappeared from North America and Western Europe, but some areas of Germany, Italy, Denmark, and Belgium continue to have suboptimal levels of iodine that require correction. ID is still present in much of the African continent, the Middle East, and large parts of Asia. It is also found in the countries of the former Soviet Union, but less is known about its extent and severity.
4. The techniques available to assess ID and IDDs include palpation of the thyroid, ultrasonographic mapping of thyroid size and structure, measurements of iodine in the urine, and assays for thyroid hormone, TSH, and thyroglobulin. Of these methods, the one currently providing the most information for epidemiological purposes and the most practicable is measurement of urinary iodine.
5. Universal iodization of salt is the most effective method for preventing IDDs. When the degree of IDDs demands a prophylactic program and iodized salt is not immediately available, iodinated oil may be given intramuscularly or orally as a long-term, interim preventative.
6. The single most important activity in programs of IDD prevention after a program has been initiated is careful monitoring. This includes measurement of

iodine in the salt from point of manufacture or entry to the consumer's table. Biological monitoring is also essential, and urinary iodine concentration is usually the preferred indicator. When facilities, skills, and resources are available, other biological monitoring is useful, such as measurements of TSH, T4, plasma thyroglobulin, and clinical status. Other important activities include general education regarding the role of iodine in health and continuing research on iodine deficiency and its prevention at the basic and applied levels.

7. Many problems impede progress toward elimination of IDDs. Political or popular support may be lacking for a variety of reasons. The salt industry may also present difficulties. Complacency and fiscal constraints may impose barriers to success or the continuation of prophylaxis.
8. By virtually any measure, the benefits to a community or country far outweigh the costs of programs.
9. Action plans directed toward minimizing IDDs include internal monitoring of national programs, periodic monitoring by an independent commission, strengthening the role of regional and country program directors, enhancing cooperation among involved international agencies, expanding communications among those involved, and securing the resources needed to put the effort on a sound financial base.

APPENDIX: ICCIDD GUIDELINES FOR ASSESSMENT OF PROGRESS TOWARD IDD ELIMINATION

A. A country with universal neonatal screening, using a sufficiently sensitive TSH assay, may be declared free of iodine deficiency if fewer than 3 percent of the newborns have TSH levels of more than 5 mU/l whole blood.

B. For countries where there is no universal newborn screening, at least two of the following three criteria should be met:

1. All salt for human and animal consumption in the regions where IDD is known or suspected is iodized at a recommended level at the factory. This will ensure that representative samples obtained regularly from retail outlets, or preferably from homes, have an iodine content sufficient to ensure a daily intake of 150 mg of iodine per person daily. [The actual requirement for the level of iodine in salt at the household level will vary, depending on the quality of salt, the prevailing climate conditions (warm-moist, warm-dry, or cool-moist, cool-dry), pack-aging (bulk sack with polyethylene lining or retail pack), storing, and the daily consumption of salt.]
2. More than 50 percent of urine samples obtained on a regular basis in a statistically valid mode have an iodine content of 100 mg/l or

greater, and more than 80 percent of urine samples have an iodine content of 50 mg/l or greater.

3. In regions where IDD has been known or suspected, the prevalence of total goiter in representative surveys of children of school-age (6–12 years old) is less than 5 percent as ascertained by competent observers, and preferably confirmed by ultrasonography, if available.

C. In addition to meeting two of the above three criteria, sustainability should be established according to the following guidelines, as applicable:

1. A national IDD program has been set up; it is responsible for continuous monitoring of the status of iodine deficiency and of iodine content of salt, according to established criteria. The responsibility also includes mandatory public reporting of IDD status at regular specified intervals (e.g., every 3 to 5 years), by designated units (e.g., the program, the Ministry of Health) that are technically competent and adequately financed.
2. The government, the private sector, and consumers have a high awareness of iodine deficiency and are committed to its sustained elimination.
3. The salt industry has the commitment, technical resources, and responsibility (frequently mandated by legislation) to sustain effective iodization of salt, including its production, distribution, and monitoring.
4. The supply of iodine for salt iodization is ensured, either through private purchase by the salt manufacturers or through the government.
5. The availability and perceived health benefits of iodized salt, despite its marginally higher cost, compel consumers to buy iodized salt rather than the noniodized product.
6. The IDD program has ready access to local and regional facilities to measure iodine levels in salt and to a central laboratory, competent to measure iodine in urine or neonatal blood TSH, or both, at affordable rates.

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Appendix: Workshop Agenda

INSTITUTE OF MEDICINE
National Academy of Sciences
Board on International Health
Food and Nutrition Board
Workshop on Micronutrient Deficiencies
5–7 December 1996
National Academy of Sciences
Cecil and Ida Green Building
2001 Wisconsin Avenue, N.W.
Washington, D.C. 20007
Agenda
Thursday, 5 December
Executive Session

8:30 a.m.–8:40 a.m.	**Welcome and Introductions** Dr. Abraham Horwitz
8:40 a.m.–9:00 a.m.	**Discussion of Potential Sources of Bias** Dr. Christopher Howson, Project Director
9:00 a.m.–9:15 a.m.	**Background, Plans, and Goals of the Conference** Dr. Horwitz, Dr. Howson, and Committee Members
9:15 a.m.–9:35 a.m.	**Break**

Plenary Session

9:35 a.m.–9:45 a.m.	**Welcome** Dr. Horwitz and Dr. Frances Davidson, USAID

Session I Orientation To The Topic: Presentation Of Prepared Papers
Moderator: Dr. Horwitz

9:45 a.m.–10:00 a.m.	**Strategies for Prevention of Iron Deficiency: Experiences to Date and Lessons Learned** Dr. Fernando Viteri—presenter Dr. Nevin Scrimshaw—rapporteur
10:00 a.m.–10:30 a.m.	Discussion
10:30 a.m.–10:45 a.m.	**Strategies for Prevention of Vitamin A Deficiency: Experiences to Date and Lessons Learned** Dr. Barbara Underwood—presenter Dr. Keith West—rapporteur
10:45 a.m.–11:15 a.m.	Discussion
11:15 a.m.–11.30 a.m.	Break
11:30 a.m.–11:45 a.m.	**Strategies for Prevention of Iodine Deficiency: Experiences to Date and Lessons Learned**; Dr. John Stanbury—presenter; Dr. John Dunn—rapporteur
11:45 a.m.–12:15 p.m.	Discussion
12:15 p.m.–12:30 p.m.	**Key Elements in the Design and Implementation of Micronutrient Interventions**; Mr. Jim Greene—presenter; Dr. Eileen Kennedy—rapporteur
12:30 p.m.–1:00 p.m.	Discussion
1:00 p.m.–2:00 p.m.	Lunch (NAS Refectory)

Session II Working Groups

2:00 p.m.–6:00 p.m.	Break-Out Groups Working Group 1: Food-Based Approaches, Including Fortification; Supplementation Dr. Reynaldo Martorell—Chair Dr. Scrimshaw—Rapporteur Working Group 2: Key Elements in the Design and Implementation of Micronutrient Interventions, Including the Importance of Research, Training, and Institution Building, and the Need for Sustainability in the Longer Term Dr. Eileen Kennedy—Chair Mr. Greene—Rapporteur
6:30 p.m.	**ADJOURN FOR DAY**

Friday, 6 December
Session II Working Groups (con't)

8:30 a.m.–11:00 a.m.	Break-Out Groups

Session III Plenary Discussion

11:00 a.m.–12:30 p.m.	Preliminary Working Group Reports and Discussion Moderator: Dr. Osman Galal Rapporteur Reports (10 minutes each) Plenary Discussion (80 minutes)
12.30 p.m.–1:30 p.m.	LUNCH (NAS Refectory)

Session IV Working Groups (continued)

1:30 p.m.–6:00 p.m.	Break-Out Groups
6:00 p.m.	**ADJOURN FOR DAY**

Saturday, 7 December
Session V Plenary Discussion

9:00 a.m.–12:00 p.m.	Final Working Group Reports and Discussion Moderator: Dr. Horwitz Rapporteur Reports (15 minutes each) Plenary Discussion (2 hrs, 30 min.)
12.00 p.m.	**CONFERENCE ADJOURNS—LUNCH PROVIDED**

Executive Session—IOM Committee

1:00 p.m.–5:00 p.m.	Discussion of Workshop Findings; Finalization of Conclusions and Recommendations on Future Policy, Program, and Research; Determination of Report Content and Structure; Report Drafting Dr. Horwitz and committee
5:00 p.m.	**COMMITTEE MEETING ADJOURNS**

Attachment A

Topics to Be Considered by the Working Groups

Working Group 1: *Food-Based Approaches, Including Fortification; Supplementation*

- What are the past approaches to the prevention of iron, Vitamin A, and iodine malnutrition that have successfully reduced deficiency/disease? Of the more recent efforts, which have been successfully "implemented?" For these programs, what have been the key elements of success? What constraints were encountered?
- For past approaches to the prevention of micronutrient malnutrition that have faltered, either in outcome or in implementation, what have been the key elements of constraint?
- What are the unresolved technical issues for iron? For vitamin A? For iodine?

- For a specific micronutrient deficiency, are some interventions more cost-effective than others? How does this vary for iron, vitamin A, and iodine, and why?
- Are there technological/scientific advances with promising applications for programs?
- Much of the literature suggests that food-based approaches to prevention of micronutrient deficiencies offer the best long-term solution. Where are examples where food-based approaches have been effective? Why haven't they been used more?
- What are the critical research needs that need to be filled to more effectively operationalize micronutrient interventions?
- What has been the experience with agricultural, fiscal, and other policies in regards to micronutrient problems, and what might be promising initiatives toward this end?
- What can be done to foster alliances among government, industry, and other parties to address micronutrient problems?
- What are the possibilities for synergy among approaches to micronutrient malnutrition?
- What can be done to promote political action to reduce micronutrient deficiencies (i.e., conduct effective advocacy to strengthen "political will")?
- What are the specific recommendations for future programmatic action?

Working Group 2: *Key Elements in the Design and Implementation of Micronutrient Interventions, Including the Importance of Research, Training, and Institution Building, and the Need for Sustainability in the Longer Term*

- What have been the key managerial, community, and household/individual-level elements that have contributed to past program success or failure? Are any of these elements unique to micronutrient interventions?
- What are the elements that are required to sustain a micronutrient intervention?
- What combination strategies—across micronutrients or across approaches (e.g., dietary counseling combined with food fortification)—have proved successful (or have faltered) and what have been the elements of success (or constraint)?
- Which combination approaches have been particularly cost-effective, and why?
- What factors have influenced the degree of political support for micronutrient interventions?
- What are the specific recommendations for future programmatic action?