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Proceedings of the Colloquium "Unlocking the Potential of the World's Children through Sustainable Fortification and Public-Private Partnership"
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Preface

This *Food and Nutrition Bulletin* supplement represents the proceedings of a colloquium on micronutrient malnutrition entitled "Unlocking the Potential of the World's Children through Sustainable Fortification and Public-Private Partnership." The colloquium was held in Cincinnati, Ohio on October 10–11, 2002 at the Procter & Gamble Nutrition Science Institute. The main objectives of the colloquium were to further an understanding of micronutrient malnutrition—particularly iron, vitamin A, and iodine deficiencies; to discuss aspects of food fortification technology and product development related to these problems; to review and discuss both controlled clinical and field efficacy trials using multiple-micronutrient–fortified dietary supplements; and to examine the current role and significant advantages of public-private partnerships to address the huge worldwide problem of micronutrient malnutrition.

The colloquium arose out of the recognition that although considerable progress has been made in the last two decades in reducing the prevalence of micronutrient deficiencies in some countries, these nutrition problems continue to create enormous challenges, especially in the context of achieving sustainable and broad-scale benefits to those affected. Interventions involving dietary diversification, fortification, and the use of particular micronutrient medicinal supplements have, in different parts of the world, had some success in addressing these problems, but it was recognized that more needs to be done.

It was hoped that a colloquium could focus on some of these problems, in part by reviewing the current situation, but also by promoting new efforts to address these problems and suggesting broad partnerships and alliances aimed at the eradication of micronutrient malnutrition. We hoped that a review of current knowledge, plus a discussion of experiences, could assist a forward movement and greater collaboration in addressing the very prevalent and important problems of micronutrient deficiencies in a variety of settings.

The first group of papers provides an overview of the problems and the role of international agencies. There are papers by recognized experts dealing separately with the problems of iron, iodine, and vitamin A deficiencies, including their prevalence and consequences. This is followed by a paper on particular developments in the area of multiple-micronutrient fortification technology that deliver both stability and bioavailability without compromising the taste and appearance of the consumed product.

There are then detailed papers on efficacy trials of multiple-micronutrient dietary supplements conducted by different groups in Tanzania and the Philippines. These show the feasibility and potential benefits of a multiple-micronutrient–fortified beverage in children and pregnant and lactating women.

This is followed by two papers by social scientists. The first is a detailed social analysis of the use of a micronutrient-fortified beverage in Tanzania. The second examines the needs, and the strategies, for communicating the benefits of micronutrient fortification in general.

Following are two papers addressing the role of alliances and the importance of public-private partnerships in addressing micronutrient deficiencies using fortification, or dietary supplements. The first uses the enormous expertise of scientists at the Micronutrient Initiative in promoting and implementing micronutrient food fortification. The second, by the executive director of the newly established Global Alliance for Improved Nutrition (GAIN), looks broadly at the problem of hidden hunger and speculates on the potentially huge role of fortification.

Finally, a paper by John Pepper, chairman of the executive committee of the Procter & Gamble Co. and a former CEO, illustrates how a major corporation can, with enthusiasm, enter a new field and play an important role while collaborating with international agencies and scientific institutions in addressing problems that adversely influence the well-being of the poorest inhabitants on earth.

In conjunction with the colloquium presentations, a number of excellent posters were displayed and

discussed by the participants. Topics included a new way of preparing affordable safe water at home (from Procter & Gamble Co.); ongoing clinical study of a micronutrient-fortified beverage (from Bangladesh); the effect of nutrition education on knowledge, attitude, and practice in a community (from the Philippines); and nutrition and dietary survey data (from China). The colloquium concluded with a far-ranging discussion covering many aspects of micronutrient malnutrition, including future research needs and strategies for controlling hidden hunger.

We wish to thank the participants who attended the colloquium, including those who presented papers, as well as all the others who enriched the discussions. We are grateful to the Procter & Gamble Nutrition Science Institute for supporting the colloquium and allowing us use of the excellent facilities at the Procter & Gamble Health Care Research Center in Cincinnati.

Michael Latham, Haile Mehansho,
and Florentino Solon
guest editors

Overview: Hidden hunger and the role of public-private partnership

Michael C. Latham

Mineral and vitamin deficiencies adversely affect the health, intellect, and physical ability of some one and a half billion people worldwide. The World Bank has estimated that for less than 0.3% of their GDP, most developing countries could rid themselves of these preventable conditions and diseases, which now cost them 5% of their GDP in lost lives, disability, and low productivity.

The world needs to give much more attention to problems of protein-energy malnutrition and poor growth in children; to parasitic, viral, and bacterial infections that cause extensive preventable morbidity and mortality; and to reductions in poverty and intolerable inequity. Nevertheless, the control of vitamin and mineral deficiencies using existing scientific knowledge and technologies offers an extraordinarily large opportunity to improve human well-being and to accelerate development at relatively low cost. Furthermore, it is something that is within our grasp to achieve in a relatively short length of time. The World Bank considers micronutrient control programs to be among the most cost-effective of all health interventions.

Essential minerals and vitamins, all necessary in very small amounts, are needed for optimum growth and health, and for the efficient functioning of the immune system, the brain, reproduction, and energy metabolism. Deficiencies of micronutrients cause harm and ill health to persons of all ages, but are most devastating to children and women of reproductive age.

At this colloquium we addressed mainly deficiencies of iron, iodine, and vitamin A, which put more than 2 billion people at risk of deficiency-related disabilities. But as discussed in the paper, "Efficacy trials of a micronutrient dietary supplement in schoolchildren and pregnant women in Tanzania," our collaborative work in Tanzania uses a dietary supplement that contains eight other micronutrients in addition to iron, iodine, and vitamin A. And my long experience

in tropical countries, particularly in East Africa, convinces me that deficiencies of some of these other micronutrients are prevalent, or occur seasonally or in times of food crises.

Although I stress again the high priority that needs to be given to poverty alleviation in countries in the south, it is clear that even serious micronutrient deficiencies are not entirely eliminated by improved incomes. It is also clear that although health services can play a very important role, they alone seldom totally alleviate hidden hunger, because the etiologies of these deficiencies are complex. This is perhaps best illustrated by the causes of anemia, which include dietary deficiencies; hereditary conditions, such as sickle cell disease; malaria and other parasitic infections, and hemorrhagic conditions.

For more than three decades the three main strategies used for the control of common micronutrient deficiencies have been the following:

» Dietary diversification, often based on consumer education, and sometimes horticulture
» Food fortification
» Medicinal supplements

All of these interventions can be relatively inexpensive and in many countries have been shown to be cost effective. But despite this, the goals set at various international meetings to reduce the prevalence of these deficiencies have not been met. A prime example is the 1990 World Summit for Children goals, which aim for, by the end of the decade, virtual elimination of iodine and vitamin A deficiencies and the reduction of iron deficiency in women by one-third. I attended the UN General Assembly Special Session on Children in New York in May 2002, and with the launching of the Global Alliance for Improved Nutrition (GAIN), there had to be recognition that the 1990 goals were nowhere near achieved, and although there had been progress in control of iodine and vitamin A deficiencies, the iron deficiency goals had lagged behind pitifully.

It is our duty to ask why. Of course, no two countries are alike, and, so, the reasons vary. But I believe there are two general sets of reasons:

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1. There are constraints related to lack of awareness (because micronutrient deficiencies can be hidden) and lack of commitment by stakeholders including governments, as well as limited infrastructure and capacity to provide education or to dispense medicinal supplements, and, in many countries, non-enforcement of regulations related to fortification.
2. The second reason for the slow progress has been too little innovation, and a rather slavish continuation of old tried (and sometimes tired) options of dietary diversification, food fortification, and medicinal supplementation. They still are important, but innovation is needed to achieve goals.

The importance of this colloquium is to examine some more innovative approaches, not only in terms of the "product" that can alleviate "the problem," but also in the alliances that can be forged and the collaborative approaches that can be used to address the persistent problems of hidden hunger—problems that we have had disappointments in controlling over the last three or four decades. Examples include the importance of public-private partnerships and true collaborative efforts involving the following groups: governments and their citizens; the commercial sector and its clients who are also citizens; international agencies, including both UN and non-government organizations; and academic institutions in both developing and industrialized countries.

Combating hidden hunger: The role of international agencies

Nita Dalmiya, MPH, and Werner Schultink, PhD

Abstract

The importance of micronutrient deficiencies or "hidden hunger" was clearly emphasized by the inclusion of specific goals on iron, vitamin A, and iodine deficiency at the 1990 World Summit for Children and other major international nutrition conferences. Significant progress has since been made toward eliminating vitamin A and iodine deficiencies, with less progress made toward reducing the burden of iron-deficiency anemia. The role of international agencies, such as the World Health Organization, United Nations Children's Fund, Food and Agricultural Organization, and World Bank in assisting countries to make progress toward the World Summit for Children goals has been very important. International agencies have played a critical role in advocating for and raising awareness of these issues at the international, regional, and national levels among policymakers and the general population. Using a rights-based approach, UNICEF and other agencies have been instrumental in elevating to the highest political level the discussion of every child's right to adequate nutrition. International agencies have also been very supportive at the national level in providing technical guidance for programs, including monitoring and evaluation. These agencies have played a critical role in engaging the cooperation of other partners, including bilateral donors, non-governmental organizations, and the private sector for micronutrient programs. Furthermore, international agencies provide financial and material support for micronutrient programs. In the future, such agencies must continue to be heavily involved in programs to achieve the newly confirmed goals for 2010.

The present paper focuses on the role of international agencies in combating micronutrient deficiencies, drawing on the lessons learned over the last decade. The first section of the paper summarizes the progress achieved since 1990, and the second section describes the specific role of international agencies in contributing to that progress.

Key words: Hidden hunger, international agencies, micronutrients, World Fit for Children, World Summit for Children

Global goals for combating hidden hunger

At the beginning of the 1990s, two global conferences took place—the World Summit for Children (WSC) in 1990 [1] and the International Conference on Nutrition in 1992, which both established for the first time specific global goals and targets for reducing micronutrient deficiencies and improving child nutrition [2]. At the WSC in New York—then the single largest gathering of world leaders—government leaders representing 71 countries committed themselves to achieving several goals, three of which were directly related to the elimination of micronutrient deficiencies in women and children. The goals were as follows: (1) reduction of iron-deficiency anemia in women by one-third of the 1990 levels; (2) virtual elimination of iodine-deficiency disorders; and (3) virtual elimination of vitamin A deficiency and its consequences, including blindness [3]. At the International Conference on Nutrition in Rome, government representatives from more than 150 states and the European economic community reaffirmed the micronutrient goals of the WSC [2].

There are good reasons why such an ambitious agenda for improving nutrition was adopted. First, there was recognition that all children have a right to adequate nutrition. This was first articulated in the Universal Declaration of Human Rights adopted in 1948, and most recently expressed in the Convention on the Rights of the Child (CRC) which has been

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Mention of names of firms and commercial products does not imply endorsement by the United Nations University.

ratified by 192 countries [4]. Second, good nutrition is recognized as the foundation for survival, growth, and development of children. Well-nourished children have improved health, perform better in schools, grow into healthy adults, and have longer life expectancy. Well-nourished women face fewer risks during pregnancy and their children start life both physically and mentally healthier. Moreover, it was recognized that fetal and infant malnutrition have the most serious and long-term consequences, particularly on the development of chronic diseases in later life. Plus, there is considerable evidence that malnutrition is a contributing factor in half of all deaths in children under 5 years of age [5]. This is true not only for severe and moderate malnutrition but also for mild malnutrition. In addition, the importance of micronutrients—particularly iodine, iron, and vitamin A—to the survival, health, and cognitive development of children had gained wider recognition.

Progress toward combating hidden hunger

The WSC also marked the first time that there was systematic follow-up and rigorous monitoring of all United Nations' (UN) conferences and summits of the 1990s. The process instituted following the WSC has provided a rich reservoir of data with which to measure the progress and the commitment of governments. In 1998, UNICEF embarked on a process of helping countries assess progress in relation to the WSC goals. A list of global indicators was developed through extensive consultation both within UNICEF and externally with other partners, such as the World Health Organization (WHO); United Nations Educational, Scientific, and Cultural Organization (UNESCO); International Labor Organization (ILO); Centers for Disease Control and Prevention (CDC); universities; and donors including the United States Agency for International Development (USAID). A special household survey—the Multiple Indicator Cluster Survey (MICS)—was specifically developed to assist countries in measuring progress toward the goals and was used in more than 70 countries to collect data on the WSC goals. In conjunction with the MICS, data collected from the USAID-funded Demographic and Health Surveys (DHS) and other national household surveys together provided a comprehensive picture of progress across the various regions and countries of the world.

Vitamin A deficiency

Significant progress was made toward several of the WSC goals for children, notably the micronutrient goals of eliminating iodine and vitamin A deficien-

cies. Estimates indicate that the global prevalence of vitamin A deficiency as measured by low blood serum levels in school-age children varied between 75 and 125 million [6]. Because of the initially slow progress toward eliminating vitamin A deficiency, an informal technical consultation on vitamin A was held in December 1997, bringing together international organizations—including WHO, the Micronutrient Initiative (MI), UNICEF, and Helen Keller International (HKI)—as well as donors (the Canadian International Development Agency [CIDA] and USAID), and leading technical experts on vitamin A deficiency (Johns Hopkins University School of Public Health, Baltimore) to discuss ways to accelerate progress. The group stressed the importance of vitamin A as an essential child-survival intervention and recommended vitamin A supplementation as a reliable and effective way to eliminate vitamin A deficiency. The group also highlighted the potential effectiveness of food fortification. The informal consultation advised all countries with an under five (children under the age of 5 years) mortality rate of more than 70 deaths per 1,000 live births to begin the distribution of vitamin A supplements immediately, regardless of whether the nation's vitamin A problem had been assessed, thus removing a constraint to progress [7].

Since 1998, rapid progress has been made toward improving vitamin A intakes using a strategy of periodic, high-dose supplementation. The number of developing countries providing at least one high-dose vitamin A supplement to 70% or more of under-fives has risen from only 11 countries in 1996, to 27 in 1998, to 43 in 1999, and to 44 in 2001 [8] (fig. 1). This was accomplished mainly due to the opportunity to combine vitamin A supplementation with the ongoing national immunization days (NIDS), which are events held with periodic frequency in countries to vaccinate children against polio. Of the 44 countries, 17 conducted two rounds of high-dose vitamin A supplementation resulting in high coverage rates,
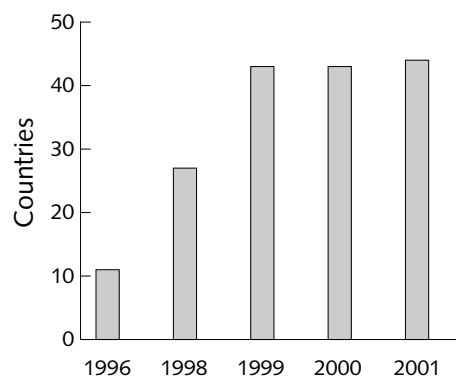

FIG. 1. "Rapid progress." Number of countries with high vitamin A supplementation coverage (one dose)

thereby achieving the goal of virtual elimination of vitamin A deficiency [8]. It is estimated that between 1998 and 2000, more than 1 million child deaths may have been prevented as a result of vitamin A supplementation [8]. It is praiseworthy that the highest coverage rates were achieved in sub-Saharan Africa and also in some of the least developed countries of the world [8]. (fig. 2).

The challenge now is to devise alternative distribution systems to effectively deliver vitamin A supplements as NIDS are being phased out in many countries. In recent years, some countries (e.g., Tanzania, Senegal, Nepal, and the Philippines) have used innovative channels such as micronutrient days and child health days to reach more than 80% coverage with two rounds of vitamin A supplements per year [8].

The global partnership that spurred action on vitamin A in the last years of the 1990s needs to be sustained, and further expansion of coverage is essential. Several countries (e.g., Zambia, Nigeria, and Kenya) have initiated vitamin A fortification of food staples such as flour and sugar with limited progress [9]. Because micronutrient deficiencies do not exist in isolation, multiple-micronutrient fortification of food staples is a more cost-effective strategy. The Global Alliance for Improved Nutrition (GAIN), an alliance of the public and private sectors, has been established and will support large-scale food fortification activities undertaken by National Fortification Alliances (NFAs) of government, industry, and other stakeholders.

A key element of achieving progress toward the vitamin A goal to date has been advocacy for existing delivery mechanisms, especially NIDS, and new efforts will need to be made around the diverse distribution initiatives that will replace the NIDS. One potential major new mechanism to improve micronutrient status is the fortification of food staples such as flour, maize meal, and sugar with a number of micronutrients, including iron, folic acid, B vitamins, and vitamin A.

Iodine deficiency

When the problems of micronutrient deficiencies were assessed at the beginning of the last decade, it was estimated that approximately 1.6 billion people or 30% of the world's population were affected by iodine deficiency due to a lack of iodine in the diet [10]. Where prevalent, iodine deficiency can significantly affect the intelligence quotient (IQ) of populations and has devastating consequences for the broader development potential of nations.

It was agreed that universal salt iodization (USI), i.e., the iodization of all edible salt including animal salt and salt used for food processing, should be the main strategy to eliminate iodine deficiency [11]. While other food products can also be iodized, salt is widely consumed and inexpensive to iodize. Salt has successfully been iodized in industrialized countries since the 1920s and therefore has a proven track record. Prior to 1990, few developing countries had large-scale salt iodization programs and it was estimated that less than 20% of edible salt was iodized [12].

Dramatic progress has been made during the last decade toward eliminating iodine deficiency. Household consumption of iodized salt more than tripled during the last decade. In 2001, 70% of households in the developing world were estimated to consume adequately iodized salt (fig. 3). The countries of Latin America and the Caribbean achieved the highest levels of iodized salt coverage (81%) followed closely by East Asia and the Pacific at 80%. The Middle East and North Africa stood at 70%, followed by sub-Saharan Africa at 68%. South Asia lags behind at 55% mainly due to slow implementation in India and Pakistan. In central and
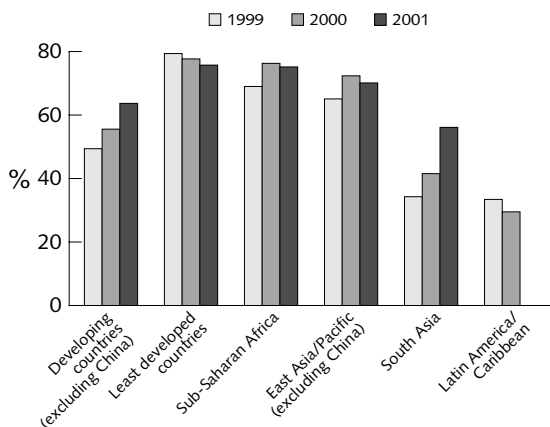
FIG. 2. Vitamin A supplementation in the developing world. Percent of children aged 6–59 months who received at least one vitamin A supplement
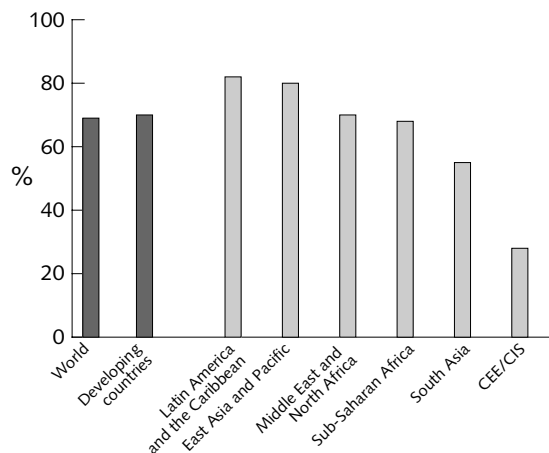
FIG. 3. Levels of iodized salt consumption (1997–2000). Percent of households consuming adequately iodized salt

eastern Europe/Commonwealth of Independent States, less than one-third (28%) of households consume iodized salt [12] (see fig. 3).

Despite this impressive progress worldwide, there are still 35 countries where less than half of the population uses iodized salt, and 41 million babies are born every year unprotected from iodine deficiency and its lifelong consequences [12] (fig. 4). It is critical that the gains made thus far are sustained and the availability and use of iodized salt increases in countries that have low coverage.

The task of sustaining iodine deficiency elimination requires constant vigilance. Experience has shown that in the absence of adequate monitoring and continued political support, iodine deficiency can resurface as witnessed in Guatemala and Bolivia [13]. It is therefore imperative that salt iodization be continually monitored along with the iodine status of the population. Strong partnerships between salt producers, governments, scientific groups, and civil society organizations at the national level will be key to ensuring that salt iodization is sustained and that iodized salt reaches everyone.

Iron-deficiency anemia

Iron deficiency is a global nutrition problem affecting the health of billions of people worldwide, with subsequent impact on the economic performance of affected nations. The WSC goal of reduction of iron-deficiency anemia in women by one-third of the 1990s levels was closely linked to maternal health. The main intervention to reduce anemia in pregnant women was the distribution of iron-folate supplements to pregnant women through the public health system. While several governments of developing countries have expanded coverage of iron supplementation using their own resources, the bulk of support for iron-folate supplementation programs comes from external resources,

such as the government of the Netherlands and the Micronutrient Initiative. Between 1993 and 1996, UNICEF supported 122 countries in distributing more than 2.7 billion iron supplements to pregnant women [14]. An additional 1 billion iron-folate tablets were distributed over the 2-year period of 1999–2000 [14]. Iron supplementation was perceived as a doable strategy because of its proven impact on anemia and because iron supplements are cheap, at a price of approximately $1.50 (US) per 1000 tablets.

Although data on the prevalence of anemia among pregnant women are lacking, it is estimated that there has been virtually no improvement in anemia status since 1990 [12]. During the mid-90s, prevalence among pregnant women in South and Southeast Asia and in sub-Saharan Africa was estimated to be approximately 50%.[15] There is, however, some evidence to show that the prevalence of severe anemia may have been reduced.

There are several reasons for the relative lack of progress in reducing the burden of iron-deficiency anemia compared with the other micronutrient goals. At the global and national level, a lack of consensus on strategies and clear advocacy messages aimed at mobilizing the donor community and key decision-makers partially accounts for the lack of progress compared with other micronutrient programs. There have been constraints at the program level, too, because iron-folate supplements have not always been available in sufficient quantity; in addition, women have failed to take supplements as recommended partly because of side effects and partly because the information provided by health staff has been inadequate and poorly communicated to them. Furthermore, most women only attend prenatal care at a relatively late stage in pregnancy, when anemia and its consequences are difficult to address. In addition, the coverage of prenatal care is extremely low in many countries. Integrated approaches that combine dietary improvements, including food fortification, supplementation of multiple micronutrients, infection control, and early prenatal care are needed. Program strategies also need to address issues to improve the care of women, especially during pregnancy, as well as to improve birth spacing. In order to have impact, it would also be important to improve the nutrition status of women before they become pregnant. A few countries (e.g., India) have already started weekly supplementation of adolescent girls in schools as a way to improve their iron status prior to pregnancy.

Reducing anemia may only be achieved through a combination of strategies. Supplementation with iron and folate during pregnancy remains an important strategy, but acceptance-related problems must be overcome. Supplementation should include other nutrients, because anemia can be due to deficiencies of other nutrients as well, including vitamin A, zinc, and
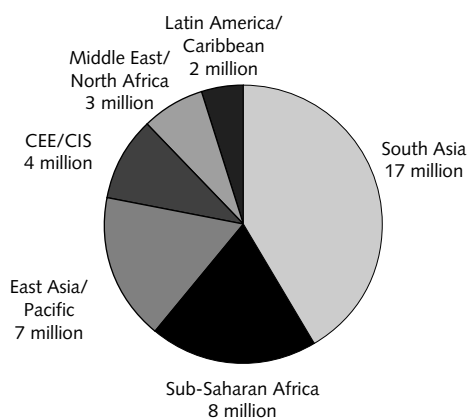

FIG. 4. Forty-one million newborns still unprotected from learning disabilities caused by iodine deficiency

vitamin B_{12}. Multiple-micronutrient supplementation, rather than iron-folate supplementation alone, is now being investigated in pilot trials as an option to reduce anemia and improve intrauterine growth. Food fortification is another strategy that needs to be pursued more rigorously, including partnerships with the food industry. Prevention of diseases, such as malaria and helminthic infection, should also be part of an overall strategy to reduce anemia. In addition, it should be recognized that anemia is highly prevalent among young children, especially in South Asia and sub-Saharan Africa. This condition has a marked negative impact on child development. Programs to address anemia in young children must also receive greater priority and should include multiple-micronutrient supplementation.

Achievements and opportunities

It is clear that while progress has been substantial toward some of the micronutrient goals—vitamin A and iodine—it has been lacking toward others. In areas where progress did occur, it was the result of strategic programmatic shifts combined with effective advocacy and effective partnerships. The availability of low-cost and technology-driven interventions, such as salt iodization and vitamin A supplementation, played an important part in the progress achieved. Furthermore, the development of clear and simple messages about the importance of these micronutrients for optimal function outcomes (e.g., iodine and brain development, vitamin A and mortality), and the feasibility and cost-effectiveness of these interventions made it easier to convince decision makers and donors alike to invest in micronutrient programs. The rapid success that followed shows that with a combination of factors—political will, availability of national/international resources, international and national partnerships, capacity development and monitoring—positive results could be obtained in a relatively short span of time. The lessons of the last decade, both the successes and failures, in addressing the WSC goals are critical in defining how the international nutrition community, governments, and our other partners move toward sustaining the gains and further reducing the burden of micronutrient malnutrition.

Finally, an important achievement of this decade has been the increased awareness of the role of nutrition in early child development as well as in human development and poverty alleviation. A major opportunity to make further progress in this regard is provided by the World Fit for Children (WFC) and the Millennium Development Goals. The WFC goals focus on reducing malnutrition in children under 5 years of age by at least one-third through supportive strategies that include the sustained elimination of vitamin A and iodine deficiencies by 2005; reduction

by one-third in the prevalence of anemia, including iron deficiency, by 2010; and accelerated progress toward reduction of other micronutrient deficiencies, through dietary diversification, food fortification, and supplementation.

The role of international agencies

In reviewing the experiences of the last decade, it is clear that international agencies such as UNICEF, WHO, MI, the World Bank, and the regional development banks played a significant role in achieving the progress described in the previous section. Specifically, international agencies were instrumental in moving the international nutrition agenda forward by their work in the several areas described below.

Advocacy, partnership, and alliance building

The global conferences and summits held in the earlier half of the decade were significant opportunities for advocacy and alliance building around the importance of micronutrient malnutrition. Both the WSC and the Conference on Ending Hidden Hunger (Montreal, 1991) were successful in creating awareness of the global problem of micronutrient malnutrition and its consequences and, in turn, triggering discussion at regional and national levels among policymakers in favor of eliminating micronutrient malnutrition. It was realized early on that in order to have an impact on micronutrient malnutrition, it would be critical to harness the technical expertise and resources of partners at all levels—international, regional, and national.

At the international level, UNICEF and Kiwanis International, a leading international service organization, entered into partnership with the goal of eliminating iodine deficiency. Kiwanis International committed itself to mobilize $75 million to support universal salt iodization (USI). Furthermore, Kiwanians around the world made a commitment to increase public awareness of the problem and consequences of iodine deficiency and to promote the use of iodized salt. This experience with Kiwanis International has once again proven the value of partnerships with civil society organizations for public health initiatives.

The Network for the Sustained Elimination of Iodine Deficiency, which was launched at a special session of the United Nations general assembly in May 2002, is another example of an "alliance" of organizations, including salt producers' associations, UN agencies, international non-governmental organizations, research institutions, civil society organizations, professional bodies, and private foundations that are all committed to fulfilling the World Fit for Children (WFC) goal on iodine nutrition. Among its various activities, the network through its member organiza-

tions supports the formation of "national watches" at the national level, bringing together government, international organizations, the salt industry, civil society organizations, and consumer groups in favor of sustained iodine deficiency elimination. Similar coalitions using this model are being formed to support other food fortification initiatives at the country level.

At the regional level, several alliances were forged and strengthened with organizations and groups, such as the South Asian Association for Regional Cooperation (SAARC), the Organization of African Unity (OAU), and the Economic Community of West African States (ECOWAS), to follow up on the commitments of the global summits and conferences. Regional technical meetings were also held to bring together key scientific groups and governments to discuss the issues of micronutrient malnutrition. Advocacy took place at the national level, bringing together scientists, civil society organizations, rights groups, government, and representatives of international organizations to galvanize public opinion around the need to tackle "hidden hunger." This advocacy in favor of micronutrients created a favorable policy environment at the national level, whereby action and programs in support of eliminating micronutrient malnutrition became possible.

Technical support for implementation of national programs

At the national level, international organizations have supported a variety of actions, such as national surveys to document the extent of the problem. These surveys have also played a useful advocacy role in convincing governments to take action. Consensus-building workshops involving the private sector were also organized at the national level by international organizations to agree on the problem of micronutrient deficiency and to decide on actions. These workshops and national debates were successful in ensuring inclusion of nutrition and micronutrients in national policy and development documents, such as National Plans of Action (NPAs) for Nutrition. Furthermore, significant efforts were made to provide technical guidance to countries on dosing, target groups, indicators, micronutrient composition, monitoring, and evaluation of impact through consultations organized by WHO and UNICEF.

Mobilization of the private sector

Equally important was the realization that some of the solutions to the micronutrient problem lay outside the public-health sector and that it would therefore be crucial to work with the private sector to make a positive impact on a population's micronutrient status. International agencies have stimulated public-

private cooperation at the international and national level on food fortification. In country after country, international agencies such as UNICEF have worked to remind producers of their "social responsibility" to iodize salt. Several meetings of salt producers were organized to bring together salt producers on a regional basis between 1999 and 2000 in Africa (Mombasa, Accra, and Dakar), Latin America (Bogota), and in eastern and central Europe/Commonwealth of Independent States (Kiev). A mini-symposium on the benefits of iodized salt was also included at the Salt2000 Symposium held in The Hague in May 2000. Similar dialogue and efforts with private industry are ongoing in other areas of food fortification, such as with sugar producers and flour millers.

The progress seen in salt iodization is testament to the success of this development approach, which recognizes the strategic importance of public-private alliances in addressing public health issues. Recently, in his address to the World Economic Forum in New York in 2002, UN Secretary General Kofi Annan encouraged the international community to look toward the Iodine Network's model for ways to make development programs more effective: "Take the case of the world's salt manufacturers. Working with the United Nations, they have made sure that all salt manufactured for human consumption contains iodine," he said.

Collaboration with pharmaceutical and food companies has meant that UNICEF and the other international agencies have been able jointly to provide solutions for the micronutrient problem. International organizations were able to engage the private sector around the need for research on fortified foods. Consequently, food companies have invested in product development and efficacy trials to determine the impact of fortified foods on improving the micronutrient status of populations, especially vulnerable groups such as children. As a result, several fortified products are now available in developing countries, such as margarine in the Philippines, oil in Pakistan, flour in India, and sugar in Guatemala and Zambia, to name a few. UNICEF also worked closely with Hoffman-La Roche, Inc. (Nutley, New Jersey, USA) on the composition and development of a multiple-micronutrient supplement (foodlet) used for efficacy trials in South Africa, Indonesia, Peru, and Vietnam.

International organizations have also been able to work with and to convince private companies in industrialized countries to take interest in the issue of food fortification in developing countries. UNICEF, the MI, and others have organized training workshops and study tours, provided practical assistance, and facilitated technology transfer for salt iodization between large companies, such as Akzo Nobel, and the salt industries in China and Tanzania. Similar examples exist for technical assistance in other areas of food fortification.

International agencies have also worked closely with manufacturers of food premixes and fortificants such as potassium iodate. Through the supply division in Copenhagen, UNICEF has worked with suppliers to secure competitive prices for potassium iodate, which has given a big boost to salt iodization programs at the national level.

Direct fundraising and leveraging of other sources of funding

In a number of countries, international agencies have provided direct financial support for start-up costs of fortification, including equipment, fortificant, and laboratory supplies. This has been possible due to their direct fundraising efforts with a variety of donors, including bilateral donors (e.g., Canada, the Netherlands, United States), Kiwanis International, MI, and the Bill and Melinda Gates Foundation. The agencies have also served as a "broker" among governments, the private sector, and lending institutions (the World Bank and regional banks) to negotiate support for micronutrient programs. Innovative credit schemes and revolving funds have been set up in several countries to assist companies engaging in food fortification to cover capital and other recurrent costs, such as a premix. Through advocacy, the World Bank and regional development banks, such as the Asian Development Bank, have been convinced to invest in food fortification programs. A multi-million dollar loan from the World Bank to China helped to restructure and upgrade the salt industry there, resulting in more than 90% of Chinese households now consuming iodized salt [16]. Similar success has also been achieved in Sri Lanka. Estimates indicate that private sector investments to salt iodization programs may have exceeded $1 billion in the last decade [17]. The conclusion is that advocacy work of international agencies created a supportive climate for increased investment and commercial loans for food fortification in developing countries.

Similarly, supplementation programs particularly related to vitamin A have received significant attention and support from the international donor community. This too has been the result of a concerted advocacy effort with donors, such Canada and the United States. During the last few years, UNICEF has been a major recipient of Canadian funds and in-kind contribution of vitamin A that have supported vitamin A supplementation programs in more than 40 countries. It is estimated that UNICEF provides about 400 million vitamin A capsules annually to various countries. Similarly, both the government of the Netherlands and the Canadian Micronutrient Initiative have been significant supporters of supplementation programs for pregnant women during 1998–2002.

Promoting a rights-based approach

International agencies have played a significant role in promoting a rights-based approach to eliminating micronutrient malnutrition. By arguing the right of all children to adequate nutrition and including its provision in the Convention on the Rights of the Child [18], international agencies have elevated the discussion to the highest political level and placed the national responsibility for ensuring that every child receives adequate nutrition on a legal footing. Furthermore, technical assistance has been provided to governments in numerous countries around the world on drafting of legislation and regulations around salt iodization and food fortification. In countries where such laws and regulations have been passed, they have served the useful purpose of creating a "level playing field" or operating standards for the food industry engaged in fortification, and have served as a method of enforcing and punishing those in the private sector who are noncompliant.

Support for monitoring and evaluation

When the micronutrient goals were endorsed at the beginning of the 1990s, there was no general agreement as to which countries had a problem of public health significance in relation to iodine or vitamin A deficiency, or on the indicators that could be used for monitoring progress toward achieving the goals. WHO and UNICEF organized a series of consultations with groups of scientists to establish a consensus on indicators and methodologies for assessment that could be recommended to countries. WHO and UNICEF also supported work to bring together existing knowledge on the prevalence of iodine and vitamin A deficiency and tabulated this information according to the newly established indicators. In 1992, WHO published a report on the global prevalence of iron-deficiency anemia in women [15].

A series of process indicators were later established against which to measure progress toward eliminating vitamin A and iodine deficiency. These process-oriented indicators allowed UNICEF and its partners a way to rapidly measure progress toward the goals at the national level. The process indicators, such as percent of under-five children receiving vitamin A supplements and percent of households using adequately iodized salt, were selected for inclusion in the large household surveys such as DHS and MICS. As previously mentioned, significant attention was paid to measuring progress toward the WSC commitments, resulting in a significant increase in the availability of data on child malnutrition, including micronutrients, at the national level. As a result of the end-of-decade survey activity, there are more than 70 countries reporting updated figures on the consumption of iodized salt at the household level (fig. 5).

Because of this attention to measuring progress, significant efforts were put into strengthening the capacity of laboratories around the world to measure micronutrients. The establishment of clear indicators by WHO greatly assisted in this process. The CDC along with several international agencies, including UNICEF, WHO, MI, and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD), recently took the lead in creating the network of the International Resource Laboratories for Iodine (IRLI). At a conference in Thailand in May 2001, it was agreed that an international network of iodine resource laboratories would strengthen the capacity of individual country laboratories to accurately measure iodine in urine and salt. Based on the recommendations of this meeting, 12 laboratories were selected from each of the 6 WHO regions on the basis of their laboratory performance, capacity and infrastructure, solid links to a national iodine deficiency disorder (IDD) programming body, and geopolitical representation. It is anticipated that in the future, the mandate of the IRLI groups of labs could either be expanded to include the other micronutrients or that other laboratories with expertise in measuring vitamin A could be included.

Conclusion

The role of international agencies—both UN agencies and international NGOs—has been pivotal, as evidenced by the progress made toward eliminating vitamin A and iodine deficiencies. With the establishment of the Millennium Development Goals (MDGs) and the micronutrient goals reaffirmed in the World Fit for Children document, there is a new opportunity for international agencies to continue making progress in these areas and to start making progress toward the reduction of iron-deficiency anemia. To do this, international agencies will need to work more closely together—each must bring its individual strengths in support of national programs but also to avoid duplication of efforts and to fill gaps.
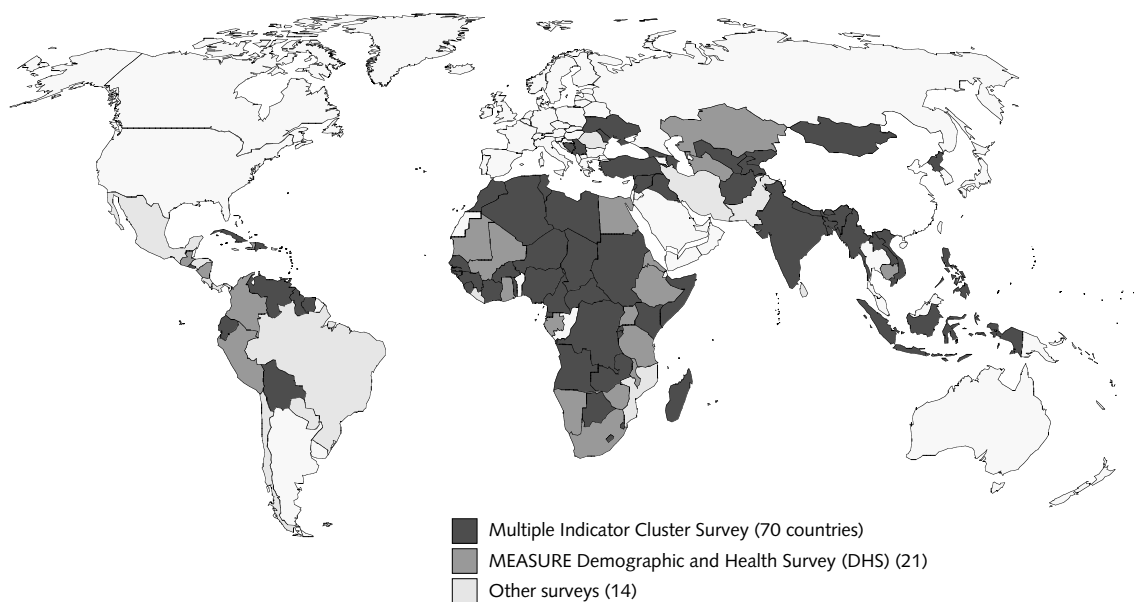
FIG. 5. End-decade household survey activity

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Vitamin A deficiency disorders in children and women

Keith P. West, Jr.

Abstract

Vitamin A deficiency is an endemic nutrition problem throughout much of the developing world, especially affecting the health and survival of infants, young children, and pregnant and lactating women. These age and life-stage groups represent periods when both nutrition stress is high and diet likely to be chronically deficient in vitamin A. Approximately 127 million preschool-aged children and 7 million pregnant women are vitamin A deficient. Health consequences of vitamin A deficiency include mild to severe systemic effects on innate and acquired mechanisms of host resistance to infection and growth, increased burden of infectious morbidity, mild to severe (blinding) stages of xerophthalmia, and increased risk of mortality. These consequences are defined as vitamin A deficiency disorders (VADD). Globally, 4.4 million preschool children have xerophthalmia and 6 million mothers suffer night blindness during pregnancy. Both conditions are associated with increased risk of morbidity and mortality. While reductions of child mortality of 19–54% following vitamin A treatment have been widely reported, more recent work suggests that dosing newborns with vitamin A may, in some settings, lower infant mortality. Among women, one large trial has so far reported a ≥ 40% reduction in mortality related to pregnancy with weekly, low-dose vitamin A supplementation. Epidemiologic data on vitamin A deficiency disorders can be useful in planning, designing, and targeting interventions.

Key words: Child mortality, maternal mortality, maternal night blindness, VADD, vitamin A deficiency, xerophthalmia

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Mention of the names of firms and commercial products does not imply endorsement by the United Nations University.

Introduction

Vitamin A deficiency remains a leading public health problem in the developing world [1], with its health consequences most apparent and severe among infants, young children, and women of reproductive age. Over the past two decades, tremendous advances have been made in developing indicators of vitamin A status, and defining the magnitude of vitamin A deficiency by region, metabolic and health consequences of deficiency that respond to adequate vitamin A intake, and approaches to effective prevention. Scientific knowledge about vitamin A deficiency and its prevention continues to be translated into effective policies and programs [2] that reflect growing resolve across governments, multilateral and nongovernmental agencies, academia, private industry, and in the community to achieve results.

Successful translation of research into policy and action requires a continuous process of "taking stock," by updating estimates of magnitude in high risk populations, clarifying disease burden associated with vitamin A deficiency, exploring improved prevention through application of epidemiologic advances, and noting promising developments in the field. In this regard, the interested reader is referred to recent, comprehensive supplements that have appeared on vitamin A deficiency and its control[1] as well as to papers that appear elsewhere in this supplement. The present paper addresses the current magnitude of vitamin A deficiency and its array of health disorders in young children and women, as a means to highlight the continued, critical importance of controlling

[1] The September 2001 (vol. 22, no. 3) issue of the *Food and Nutrition Bulletin* (Special Issue on Vitamin A Supplementation and Control of Vitamin A Deficiency) and the September 2002 (vol. 132, no. 9S) issue of the *Journal of Nutrition* (25 Years of Progress in Controlling Vitamin A Deficiency: Looking to the Future. Proceedings of the XX International Vitamin A Consultative Group Meeting) are dedicated to vitamin A deficiency and its control.

this micronutrient deficiency in disadvantaged populations.

Prevalence and burden of vitamin A deficiency

Estimates of extent and severity of vitamin A deficiency are imperfect, as they depend on the frequency of use of valid indicators of vitamin A status across populations, and draw on diverse sources of data of varying representativeness. In chronically deficient regions, reports that are based on xerophthalmia in children [3] and night blindness in pregnant women [4] can provide highly specific data on moderate-to-severe vitamin A deficiency. Dark adaptometry provides a recently standardized, valid approach to quantify the prevalence of mild scotopic vision loss attributable to vitamin A deficiency [5] but has been insufficiently used to date for estimating burden of deficiency. Stable isotope use allows measurement of total body stores of vitamin A and validation of other indicators of status [6], while the relative dose response remains a useful research tool for indirectly assessing hepatic retinol adequacy [7]. However, assessing liver or total body stores of vitamin A by these means remains difficult, expensive, and little used in large population studies. Although new and simpler assessment tools are being developed, determination of vitamin A deficiency in most populations rests on interpreting distributions of retinol content of serum or plasma [8, 9] and, among women, also in breast milk [10]. Conjunctival impression cytology (CIC) has also found wide use in assessing population prevalence of vitamin A deficiency [5], particularly when serologic data could not be collected. These latter measures of status have been used by the World Health Organization (WHO)

[11, 12], the Micronutrient Initiative (MI) [13, 14], and the International Vitamin A Consultative Group (IVACG) [15] to estimate or monitor changes in the burden of vitamin A deficiency in children and, more recently, estimate the extent of deficiency in pregnant women [15].

Presently, the IVACG conservatively estimates there to be 127 million vitamin A-deficient preschool-aged children, defined as serum retinol (SROL) concentration < 0.70 µmol/L (< 20 µg/dl) or abnormal CIC, in the developing world,* of whom 4.4 million have xerophthalmia (X)**(table 1) [15]. Nearly half of the world's xerophthalmic children reside in South and Southeast Asia, of whom over 85% live in India. These numbers are comparable in magnitude to those of a decade ago [16] despite considerable population growth during the interim, which probably reflects degrees of success in vitamin A deficiency control. Figure 1 presents a map of regional preschool child risk of both xerophthalmia (all active stage, X), at cut points of 0.5% and 1.5%,*** and vitamin A deficiency (< 0.70 µmol/L for serum retinol or abnormal impression cytology) [15] using 15% as a prevalence cut point as recently adapted by the IVACG [2]. Accordingly, highest risk countries where xerophthalmia affects > 1.5% and vitamin A deficiency > 15% of young children include especially India, and countries in the northeast and Horn of Africa. Several countries have lower rates of xerophthalmia with persistent (biochemical) vitamin A deficiency (e.g., Bangladesh and Nepal), possibly reflecting known high efficacy of vitamin A capsule distribution in preventing xerophthalmia (≈ 90%) but relative inability to raise and sustain adequate serum retinol concentrations

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* Includes an estimate of 45,000 children in Macedonia, based on a recent national survey [15].

** Including active stages of night blindness, Bitot's spots, and corneal xerophthalmia [3].

*** 0.5% represents the minimum prevalence for Bitot's spots to reflect public health significance [2] and 1.5% the sum of public health minima for night blindness and Bitot's spots combined.

Table 1. Prevalence and numbers of vitamin A–deficient and xerophthalmic preschool-aged children by region

Region	Population < 5 years old (thousands)	Vitamin A deficient (Serum retinol < 0.70 µmol/L or abnormal impression cytology)		Xerophthalmia	
		%	No. (thousands)	%	No. (thousands)
Africa	103,934	32.1	33,406	1.53	1,593
East Med	59,818	21.2	12,664	0.85	510
S/SE Asia	169,009	33.0	55,812	1.20	2,026
West Pacific	122,006	14.0	17,128	0.18	220
Americas	47,575	17.3	8,218	0.16	75
East Europe	152	29.6	45	0	0
Total	502,494	25.3	127,273	0.88	4,424

Source: West KP Jr. [15]
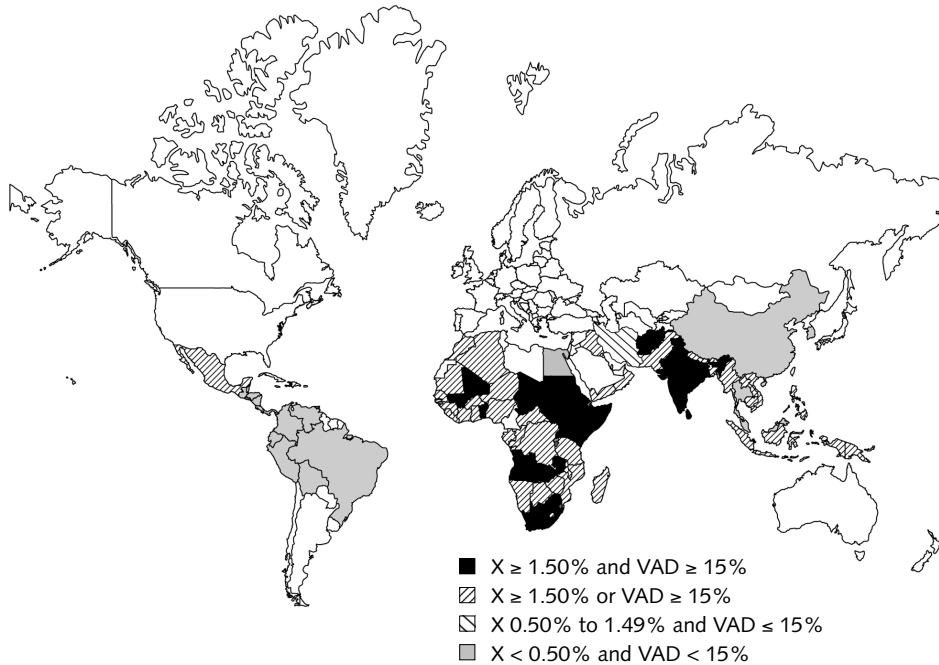
FIG. 1. Global distribution of preschool vitamin A deficiency (VAD), defined by serum retinol concentrations < 0.70 µmol/L or abnormal impression cytology and all active stages of xerophthalmia (X) at cutoffs that recognize recent IVACG recommended cutoffs. Source: West KP Jr. [15] *Reprinted with permission from the American Society for Nutritional Sciences*

in populations [17]. Linking vitamin A distribution, for example, with the Expanded Programme for Immunization (EPI) and National Immunization Day (NID) activities [18] has achieved considerable success in many countries in raising once-annual vitamin A coverage, which may have lowered the xerophthalmia burden further in the past few years.

Chronic vitamin A deficiency appears to affect women during their reproductive years. Recently, it has been estimated that nearly 20 million pregnant women in a given year have low vitamin A status (with SROL or breast milk vitamin A concentrations < 1.05 µmol/L),

of whom 7 million are deficient (concentrations < 0.70 µmol/L) and 6 million experience gestational night blindness (XN) [15] (table 2). By these estimates, nearly two-thirds of the world's night-blind women live in South and Southeast Asia, of whom 75% live in India, although this provisional global distribution may be reflecting, to a degree, more adequate population assessment of maternal XN in India than other high-risk countries at present for which conservative assumptions were applied to obtain numbers of cases.

The large numbers of vitamin A–deficient pregnant women also suggest that interim school-aged and ado-

Table 2. Prevalence and numbers of vitamin A–deficient and night-blind pregnant women by region

| Region | Live births per year (thousands) | Vitamin A Status (based on serum/breast-milk vitamin A concentration) | | | | Night blindness | |
| | | Deficient (< 0.70 µmol/L) | | Low (< 1.05 µmol/L) | | | |
		%	N (thousands)	%	N (thousands)	%	N (thousands)
Africa	24,425	10.0	2,453	22.0	5,383	4.4	1,075
East Med	12,003	7.8	938	17.5	2,095	3.2	384
S/SE Asia	36,212	6.2	2,251	24.3	8,797	10.9	3,931
West Pacific	24,806	5.0	1,240	10.9	2,702	1.9	467
Americas	9,967	3.8	375	8.0	799	3.8	376
Total	107,413	6.8	7,257	18.4	19,776	5.8	6,233

Source: West KP Jr. [15]
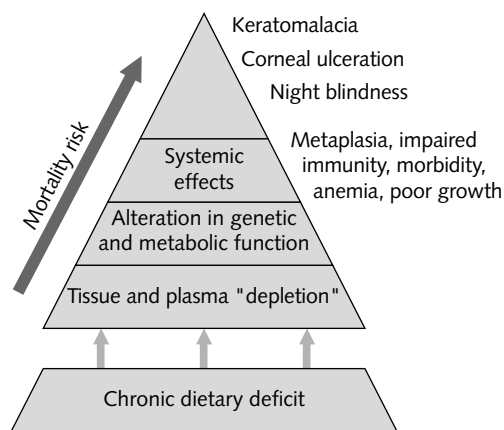
FIG. 2. Conceptualization of vitamin A deficiency disorders (VADD). Chronic dietary deficit is not a VADD, but a chronic, underlying cause that gives rise to vitamin A-deficient tissues and consequent disorders. Source: West KP Jr. [15] *Reprinted with permission from the American Society for Nutritional Sciences*

lescent years, at least among females, are ones likely to harbor significant, but as yet little appreciated, vitamin A deficiency.

Vitamin A deficiency disorders (VADD)

Health consequences attributable to vitamin A deficiency are collectively defined as vitamin A deficiency disorders, or VADD (fig. 2), as recently set forth in the Annecy Accords [2]. These conditions range from ocular manifestations of xerophthalmia, including its blinding sequelae, to less specific disorders of impaired mechanisms of host resistance, severe infectious illnesses, poor growth, and mortality attributable to vitamin A deficiency in a population [2]. The stages of xerophthalmia, owing to their specificity, comprise both VADD and indicator variables for assessing prevalence and severity of deficiency in a population. On the other hand, biochemical concentrations of retinol in plasma, breast milk, or the liver below conventional cutoffs serve to indicate status, but, alone, do not constitute VADD. Long-term inadequate dietary intake influences vitamin A status and is a strong determinant of VADD [19, 20], but, by itself, assessed dietary vitamin A intake serves neither as a status indicator nor disorder. The inclusive, but plausible, evidence-based definition of VADD provides a framework for improving status assessment, better understanding vitamin A deficiency–disease relationships and their associated health burden, and characterizing public-health benefits of prevention.

VADD in preschool children

Preschool children in poor societies are especially

susceptible to vitamin A deficiency and its health consequences (xerophthalmia, infection, poor growth, anemia, mortality) due to high nutrient demand to support growth, frequent exposure to infection and nutritionally demanding illnesses, and chronic lack of an adequate diet and health care.

Xerophthalmia

Xerophthalmia remains the leading known cause of preventable blindness in young children [1, 21]. Corneal xerosis, ulceration, and necrosis (keratomalacia) are the result of severe vitamin A deficiency, often precipitated by severe infection such as measles [22] in the presence of wasting malnutrition [23]. Corneal xerophthalmia, however, is rare, due to combined effects of low incidence and high case fatality, and appears to be in decline [24]. Milder, non-blinding xerophthalmic stages include night blindness, reflecting impaired dark adaptation due to lack of vitamin A in rod photoreceptors, and Bitot's spots arising from keratinizing metaplasia of the bulbar conjunctiva [3]. Both conditions are indicative of moderate to severe vitamin A deficiency, with affected children usually having serum retinol concentrations below the conventional cutoff of 0.70 µmol/L [25]. Xerophthalmia responds to high-potency vitamin A treatment,* with night blindness typically resolving within 24–48 hours, Bitot's spots responding within several days to a few weeks, and corneal lesions beginning to heal within 2–3 days [3].

Infectious diseases

Vitamin A deficiency increases susceptibility to infection, which, in turn, may further aggravate the deficient state, revealing a classical "synergism" described by Scrimshaw, Gordon, and Taylor [27] almost four decades ago that our increased understanding of mechanisms continues to support [28–30]. Children with mild xerophthalmia (night blindness or Bitot's spots) exhibit impaired antibody [31] and cell-mediated [32] immunity, elevated acute phase plasma proteins suggestive of infection [33], poor growth [34, 35], in addition to increased risks of diarrhea [36, 37], respiratory disease [36], and mortality [38]. Conversely, children with diarrhea and lower respiratory infection living in areas of endemic vitamin A deficiency are more likely to develop xerophthalmia [39]. The reverse causality is plausible given high urinary losses of retinol following enteric and respiratory infections [30] and acute depression of circulating retinol in response to infection [30]. These responses, coupled with decreased vitamin A intake and absorption, act to deplete tissue

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* WHO/IVACG recommends treating cases of active xerophthalmia with 200,000 IU VA on presentation, the next day and 2 weeks later; half-doses for infants 6–11 months and quarter-doses for infants < 6 mo of age [26].

retinol that can result in health consequence.

Vitamin A supplementation has been shown to reduce the severity of measles, malaria, and diarrhea. Clinical trials have shown that supplementation can reduce the severity of measles complications [40] and markedly lower case fatality, by ≈ 50% [1]. Infection with *Plasmodium falciparum* depresses serum retinol and retinol binding protein concentrations during the acute response to infection [41], which may exacerbate disease. In a randomized field trial in Papua New Guinea, supplementing preschool children with 200,000 IU vitamin A every 4 months reduced *falciparum* malarial episodes by 30%, as well as circulating parasite densities and rates of splenomegaly compared to placebo receipt [42]. Because not all studies have shown similar effects [43], additional studies are needed to confirm the prophylactic value of vitamin A against *falciparum* malaria.

Diarrhea and *shigella* dysentery are associated with increased urinary losses of retinol [30, 44], which may exacerbate infection. Vitamin A supplementation has been shown to reduce the severity of diarrhea or dysentery in undernourished populations [45–47], presumably by enhancing epithelial repair and function in the intestine and helping to conserve body stores of vitamin A. On the other hand, despite known damage that experimental vitamin A deficiency causes to respiratory epithelium and local secretory defenses in animals [48], and increased urinary retinol loss during acute lower respiratory infections (ALRI) [1, 30] and higher risks of respiratory infection in vitamin A–deficient children [1], high-potency vitamin A use has usually been found to be ineffective in reducing the incidence, duration, severity, or case fatality of ALRI in preschool children [45, 49]. In some trials, signs and symptoms of increased respiratory disease have followed vitamin A supplementation [47, 50, 51], possibly reflecting enhanced immune-mediated airway activity, inflammation, or transient toxicity [30, 51]. Adverse effects of vitamin A supplementation, when reported, have tended to occur surprisingly more frequently in adequately nourished groups of infants and children, whereas therapeutic and prophylactic benefit accrues more visibly in poorly nourished or diseased individuals or populations [1, 47, 50, 52, 53]. Mechanisms to adequately explain these interactions are presently lacking.

Poor growth

Vitamin A is essential for mammalian growth [54]. Although vitamin A is doubtless needed for child growth, isolating its effects amidst other growth-limiting insults (coexisting nutrition deficiencies or infection) has proven difficult. Children with mild xerophthalmia are often stunted [1, 37] and may exhibit some degree of wasting [37, 55]. Incident or chronic mild xerophthalmia is associated with slowed pon-

dostatural growth, but the dominating height deficit observed in cross-sectional studies may, in part, result from more complete catch-up in weight than height during recovery from one or more xerophthalmic episodes in the preschool years [34]. The more severe the vitamin A deficiency or illness, the greater the chances that supplementation will improve either linear [35, 56, 57] or ponderal [40, 57–60] growth. Effects where present, however, may be seasonal [35, 59], age- or sex-specific [57, 58, 60, 61], and may be modulated by disease factors, such as duration of respiratory infection [62] or intestinal worm burden [61], which makes the growth response difficult to predict as a public health benefit of vitamin A deficiency control. The often-noted lack of impact of vitamin A supplementation on child growth in diverse populations [63–65] may reflect relative adequacy of pre-existing dietary vitamin A intake to support levels of growth possible in a particular setting, modulating effects by other nutrition deficiencies on growth or vitamin A utilization, persistent infection, adequacy of health care, or study design factors that could mask effects (e.g., exclusion criteria, duration of study).

Anemia

A link between anemia and night blindness has been recognized since the late 19th century [66]. Since then, children with xerophthalmia have been noted to be anemic, and experimentally vitamin A–depleted animals have been found to lack hematopoietic capacity. Childhood surveys in undernourished populations of South Asia, Africa, and Central America have noted correlations (r) of ≈ 0.20–0.50 between hemoglobin and plasma retinol concentrations. The association appears causal as trials among preschool- and school-aged children have usually, though not always, reported increases in hemoglobin (Hb) concentrations following vitamin A supplementation, ranging from 9 to 21 g/L, compared with controls [66, 67]. Hematopoietic responses to vitamin A are likely influenced by initial vitamin A, iron, and parasite status of children; dosage of vitamin A; duration of supplementation; and other complex physiologic factors. Anemia of vitamin A deficiency may be attributed to several plausible mechanisms that may respond to improved vitamin A nutriture, including impaired mobilization and transport of body iron, disturbed erythropoietin synthesis, defective hematopoiesis in bone marrow, or sequestration of iron in response to acute and chronic infection [66, 67].

Child mortality

There is consistent evidence that an increased intake of vitamin A, achieved by supplementation or food fortification, can improve survival of older infants and preschool aged children. On the other hand, vitamin A supplementation below 6 months of age may or may

not improve early infant survival, which is presently driving public health research.

Infants and children 6–72 months of age. Motivated by observations in the late 1970s of higher mortality risk among mildly xerophthalmic children [38], eight community trials involving more than 177,000 preschool aged children were carried out in the 1980s and 1990s in Southern Asia and Africa to examine the effects of vitamin A supplementation in reducing mortality among preschool children. Six trials observed statistically significant reductions in mortality from all causes in vitamin A–supplemented children compared with children in control groups. Interventions that have been tested include periodic high-potency vitamin A delivery (200,000 IU in infants > 12 months old, half-dose in infants 6–11 months old, every 4–6 months), which reduced death rates by 19–34% [68–71]; weekly low-dose (8,000 IU) vitamin A delivery that lowered mortality by 54% in one trial [72]; and fortification of monosodium glutamate, a flavor enhancer, that reduced mortality by 45% when consumed by preschoolers at a level that provided approximately one-third of a recommended dietary allowance (RDA) [56] (fig. 3). The findings suggest that consuming vitamin A in smaller, more frequent doses through diet or supplements could be more protective, albeit programmatically more demanding, than periodic use of high-potency vitamin A. Although two field trials failed to find a significant impact of vitamin A on survival [73, 74], published meta-analyses have suggested that the effects of these trials are compatible with an underlying reduction in preschool child

mortality of 23–34% [1, 75, 76]. The findings are most relevant to underdeveloped settings where children are chronically exposed to undernutrition, where high levels of morbidity are coupled with inadequate health care and other social services, and where a resultant excess of childhood mortality exists.

Infants < 6 months of age. In infants under 6 months of age living in high risk conditions, improved survival with vitamin A may depend on several key factors, such as age at dosing, size of dosage, dominant causes of mortality, and possibly, body size of the infant. Placebo-controlled field trials in Nepal, Ghana, Peru, and India have, for example, failed to find an overall survival benefit among infants dosed at varying ages during the first 6 months of life. In the Nepal study, infants given placebo or 50,000 IU vitamin A (if < 1 month of age) or 100,000 IU (if 1–5 months of age) during four monthly home visits showed no differences in mortality [52]. Similarly, in the other countries, no mortality differential was observed among infants given placebo versus 25,000 IU vitamin A at each diphtheria-pertussis-tetanus (DPT) vaccine visit carried out at approximately 6, 10, and 14 weeks of age [77]. Dosing mothers with vitamin A has also achieved little improvement in early infant survival. Again, in Nepal, a randomized trial found that dosing women each week with placebo versus an equivalent of a maternal RDA of vitamin A, either preformed or as beta-carotene, had no overall impact on infant mortality [78], although subgroup analyses revealed some survival benefit to infants born of night-blind mothers [79].

The above findings suggest neither maternal nor direct dosing of infants < 6 months of age with vitamin A can improve infant survival, although liver vitamin A stores are likely to benefit for meeting subsequent demands [80–82]. However, two recent randomized, placebo-controlled trials in Indonesia [83] and southern India [84] challenge this conclusion. In both trials, infants dosed with approximately 50,000 IU of vitamin A shortly after birth, rather than later in neonatal or postneonatal life, experienced significant 64% and 22% reductions in mortality, respectively, relative to controls (fig. 4, panels A and B). Mechanisms for how vitamin A given at birth could reduce risk of death not achieved in later months or via the mother are likely to be complex, but could involve direct effects of the vitamin on organ development and maturity in the newborn that could affect subsequent function and health. For example, experimental studies in various species show that vitamin A can alter maturation, repair, or function of the immature pulmonary tract [85, 86], cardiovasculature [87, 88], immune system [89], and gastrointestinal tract [90]—problems that would be more prevalent and acute in preterm infants, who are also at higher risk of having extremely low vitamin A stores [91]. Notably, in the South Indian
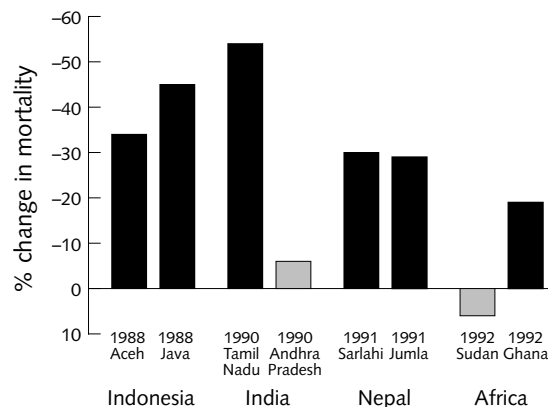

FIG. 3. Percent reductions in preschool child mortality attributed to vitamin A supplementation or fortification obtained from eight large field trials in Southern Asia and Africa between 1982 and 1992. Dark bars denote statistically significant reductions in child mortality with vitamin A. Source: Sommer A, West KP Jr. [1]. From *Vitamin A Deficiency: Health, Survival, and Vision*, by Alfred Sommer and Keith P. West, copyright 1996 by Oxford University Press, Inc. Used by permission of Oxford University Press, Inc.
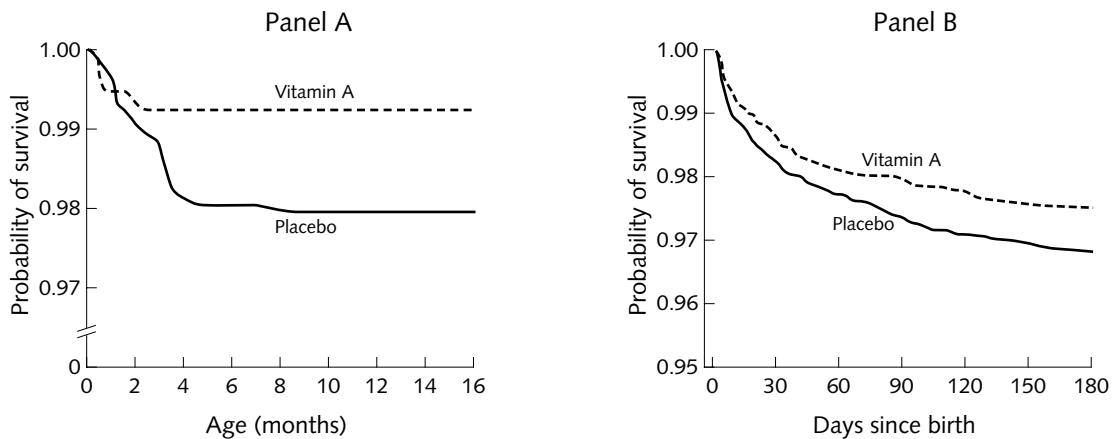
FIG. 4. Panel A: Survival curves from birth into the second year of life for Indonesian newborns randomized to receive vitamin A (50,000 IU) or placebo. Spread between lines represents a 64% reduction in mortality attributed to vitamin A receipt. Source: Humphrey JH, et al. [83]. Reprinted from the *Journal of Pediatrics*, with permission from Elsevier.

Panel B: Survival curves from birth through 6 months of age for South Indian newborns randomized to receive vitamin A (24,000 IU on 2 consecutive days) or placebo. Spread between lines represents a 22% reduction (*p* = 0.02) in mortality attributed to vitamin A receipt. Source: Rahmathullah L, et al. [84]. Reprinted from the *British Medical Journal*, with permission from the BMJ Publishing Group.

trial, the entire effect of vitamin A dosing on mortality occurred in newborns of low birth weight (< 2500 g), some proportion of whom would have been born preterm and developmentally less mature than term infants. Vitamin A–dosed newborns were also half as likely as controls to be carrying pneumococcal bacteria in nasopharyngeal secretions between 2 and 4 months of age (odds ratio [OR] = 0.51; 95% CI: 0.28–0.92) [92], suggesting reduced bacterial adherence, seen previously in vitamin A–deficient children [93], and improved resistance to pneumonia in the first half of infancy.

VADD in pregnant and lactating women

Evidence is emerging to reveal that maternal vitamin A deficiency is associated with significant health risks. Night blindness is a xerophthalmic symptom that can affect 5–15% of pregnant women in an undernourished population. Maternal history of night blindness also serves as an indicator of vitamin A deficiency among women of reproductive age and in the community, with a minimum cutoff set at 5% [4]. In Nepal, mothers reporting to be night blind in the third trimester were more likely to be anemic (odd ratio [OR] = 3) and report symptoms of urinary or reproductive tract infection (OR = 2.1), diarrhea or dysentery (OR = 3.4), or nausea, vomiting, and poor appetite (OR = 2.1) [94]. Cases were also more likely to have reported symptoms consistent with urinary/reproductive tract infection (OR = 1.9), upper gastrointestinal upset (OR = 2.7), and pre-eclampsia 2–3 months before their first report of night blindness [94]. These cases were at about the

same mid-gestational age as mothers from another prospective series, who themselves developed night blindness later in pregnancy and who were found to have lower mid-pregnancy serum retinol, retinol-binding protein, and transthyretin concentrations than women never experiencing the condition [95]. While infection may have contributed to the hyporetinolemia [30], it is likely that chronic vitamin A deficiency preceded infection, because it has been observed that night blindness tends to recur during repeated pregnancies [96]. Studies from Nepal have also revealed a four-fold higher mortality among women who had developed night blindness during pregnancy for up to 2 years following the index pregnancy outcome, primarily associated with infectious causes [97]. Thus, maternal night blindness appears to flag mothers who are vitamin A deficient and at increased risk of poor health possibly due, in part, to underlying vitamin A deficiency and other associated causes.

Milder, non-xerophthalmic vitamin A deficiency in mothers also appears to contribute to anemia. In the plains of Nepal, 14% of all maternal anemia (Hb < 110 g/L) and 29% of moderate-to-severe anemia (Hb < 90 g/L) could be attributed to low vitamin A status (SROL < 1.05 µmol/L) [98]. Low-dose, daily supplementation of pregnant Indonesian women with vitamin A (2400 µg retinol equivalents [RE]) for 2 months raised Hb by 6 g/L over placebo recipients, versus a 10 g/L increment obtained with iron alone (60 mg/d) and a 15 g/L increment when both iron and vitamin A were given, reflecting a role for vitamin A alone and in combination with iron in preventing anemia [99]. Similar additive effects of vitamin A on hema-

tologic indicators in pregnancy have been observed elsewhere [66, 67].

Vitamin A may also contribute to overall maternal health and survival. A large trial among approximately 22,000 pregnant Nepalese women observed reductions of 40% and 49% in mortality related to pregnancy through 12 weeks post-partum among those supplemented weekly with an RDA equivalent of preformed vitamin A (7000 µg RE) or beta-carotene (42 mg), respectively [100]. "Verbal autopsy" interviews conducted with family members of deceased women were inconclusive about causes of death most affected by the intervention, with some evidence of lower mortality associated with infection (by 22%, not significant) and various obstetric conditions (by 27%, not significant). Vitamin A–supplemented women reported approximately 10% fewer days of symptomatic morbidity in the third trimester of pregnancy, labor of about 1 hour shorter duration, and, in the 6 months following birth, approximately 15% fewer weekly episodes of diarrhea (OR = 0.80 to 0.87) [101].

It is plausible to suspect that vitamin A deficiency may predispose mothers to infection [102]. A trial in London in 1931 reported 77% and 38% reductions in incidence of puerperal sepsis and milder postpartum febrile episodes, respectively, among mothers who took a vitamin A (and vitamin D) preparation daily (equivalent to approximately 1 oz cod liver oil) from the last month of pregnancy through delivery [103]. This finding was recently corroborated by a 2 × 2 factorial trial that evaluated health effects of daily zinc or vitamin A (2400 µg retinol equivalents) supplement use among 680 Indonesian mothers from the first trimester of pregnancy through the early postpartum period. Vitamin A recipients were less likely to report at least 1 day of post-partum fever (> 38°C) (1.2%) than women not receiving vitamin A (5.6%) (relative risk [RR] = 0.22; 95% CI .08–.65) [104]. Zinc supplementation had no effect, nor was there interaction of the two supplements on puerperal fever. Additional trials are currently underway (e.g., in Bangladesh) to further evaluate effects of low-dose maternal vitamin A supplementation on pregnancy-related morbidity and mortality.

Prevention of vitamin A deficiency

Vitamin A deficiency can be controlled as a public health problem by maintaining adequate intakes of the nutrient in high-risk groups through direct supplementation, fortification, agronomic programs, marketing, and educational efforts to improve diet. The epidemiology of VADD, particularly well-described for mild xerophthalmia [1, 105], can provide a basis for targeting and program design. For example, the prevalence of mild xerophthalmia in children may increase seasonally with cases tending to cluster

by province, village, and within households [106]. Taking both of these time and location factors into consideration, six monthly, high-potency vitamin A supplements (e.g., 200,000 IU for children ≥ 12 months; half this dose at 6–11 months of age) [107] should be timed to precede the peak xerophthalmia season by at least a month. High vitamin A supplementation coverage has been achieved in recent years through the conduct of well-coordinated campaigns occurring every six months. National Immunization Days (NIDS) that include polio vaccination, for example, have provided opportunities to cover preschoolers once a year [18]. Often NIDS-based vitamin A delivery has been complemented by vitamin A distribution through other child health or stand-alone campaigns during alternating six-month periods [26]. For smaller programs, knowledge that VADD clusters by a factor of ~2 within villages and a factor of 7–10 among siblings of the same household [106], who tend to consume diets similar to cases [108], suggests that health care providers should do the following: (1) treat the xerophthalmic child (or night-blind mother) [3]; (2) dose prophylactically preschool-aged siblings of the case (or young children of a night-blind mother); (3) evaluate and provide dietary advice to the family of a case; and (4) broadly implement supplementation, gardening, or counseling programs in communities from which cases originate.

Nutrition education, social marketing, and other food-based approaches can be equally developed from epidemiologic evidence. Guiding mothers to breast-feed infants through the third year of life rests on a consistent association of protection against xerophthalmia [1, 109]. A diet that regularly provides preformed vitamin A or provitamin A carotenoids is strongly associated with protection from VADD among children [19, 20, 55] and pregnant women [94]. Thus, dietary counseling, guided by seasonal availability and cost, should strive toward higher consumption of vegetable, fruit, and animal sources of vitamin A. Recently it has been amply demonstrated that provitamin A carotenoids from plant foods, and especially dark green leaves, are bioconverted to vitamin A much less efficiently (≥12:1) than previously thought (6:1) [110, 111]. While such evidence should not dampen efforts to promote intakes of vegetables and fruit to improve vitamin A status, it does help explain the persistence of vitamin A deficiency amidst dietary ecologies of seasonally available provitamin A–rich foods and highlights a preference for some preformed dietary vitamin A, either from animal foods or through fortification.

Vitamin A–fortified food-aid commodities, such as those distributed as part of the United States Public Law 480 Program, often, by program design, end up "self-targeting" vulnerable groups, including those at risk of VADD during periods of nutrition stress [112].

Attention is increasingly being paid to developing, evaluating, and promoting vitamin A–fortified commercial food products that do, or could, penetrate markets of the poor, such as sugar [113], non-refrigerated margarine [114], wheat flour [115], and beverages [116], among others. Although socioeconomic indicators generally show poor specificity with vitamin A status, communities of low socioeconomic status nonetheless tend to harbor significant vitamin A deficiency in at-risk countries [1], making such fortification projects "progressive," as long as the products are priced to sell in rural and other markets serving the poor. Development of lowest-cost packaging may prove to be essential for successful vitamin A fortification of products in low-end markets.

Conclusion

Vitamin A deficiency remains widely prevalent in the developing world. In children, it leads to VADDs, which include xerophthalmia with its potential to blind; impaired host resistance to infection with consequent increased risks of severe diarrhea, measles, malaria, and other febrile illnesses; poor growth; and mortality. Prevention of vitamin A deficiency and its disorders can have a marked effect on child health and survival. Although involving seemingly more complex explanatory mechanisms, vitamin A supplementation at birth may improve chances of survival during early infancy. In recent years, public health attention has been extended to reveal a sizeable burden of vitamin A deficiency among women during pregnancy and postpartum periods, with a potentially significant impact of prevention on maternal morbidity and mortality. These latter findings, while requiring confirmation, suggest a need to develop effective preventive approaches that cover these previously unappreciated target groups, thereby widening the proportion and numbers in need of vitamin A in undernourished societies. Dietary policies to prevent vitamin A deficiency should be evidence-based, marketed to high-risk populations, adequate in coverage, and flexible in program content.

Acknowledgment

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Iodine deficiency: Consequences and progress toward elimination

Glen F. Maberly, David P. Haxton, and Frits van der Haar

Abstract

While traditionally associated with cretinism and goiter, iodine deficiency has broad effects on central nervous system development that can occur in the absence of either condition. Any maternal iodine deficiency results in a range of intellectual, motor, and hearing deficits in offspring. This loss in intellectual capacity limits educational achievement of populations and the economic prowess of nations. Progress made since the historic World Summit for Children in 1990 has been outstanding. Approximately 70% of households in the world used iodized salt by 2000, compared with less than 20% in 1990. It is estimated that at least 85 million newborns out of 130 million annual births are protected from a loss in learning ability that would otherwise have occurred. The elimination of iodine deficiency, by expedient production, marketing, and universal consumption of iodized salt, represents a significant development effort in public nutrition. Although globally iodine nutrition has greatly improved, 20% to 30% of pregnancies and thus newborns still do not fully benefit from the use of iodized salt. Countries where success is in evidence could rapidly revert back to deficiency if vigilance is not maintained. Just as success came through concerted public-private-civic actions, making sure that this is expanded and will steadily go on requires continuous collaboration.

Key words: Brain development, elimination of iodine deficiency disorders, iodine deficiency, salt iodization, sustained iodine nutrition, thyroid hormone action

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Consequences of iodine deficiency

The trace nutrient iodine is of fundamental importance in human biology. Iodine deficiency is particularly damaging during pregnancy, because it retards fetal development, especially development of the brain [1, 2]. Through the past millennia, the loss of human intellectual, physical, and social potential caused by iodine deficiency has been enormous [3, 4].

The thyroid gland requires iodine for biosynthesis of the thyroid hormones thyroxin (T4) and triiodothyronine (T3). Iodine available to form thyroid hormones is dependent upon iodine intake from foods as well as interaction with possible goitrogens—other food substances that may interfere with the ability of the thyroid gland to make thyroid hormones and/or increase urinary iodine excretion. Soils are generally deficient in iodine, so iodine needs to be added to the diet to achieve sufficiency. With adequate iodine intake the inhibiting effect of most goitrogens can usually be overcome. Normal development of the central nervous tissues is dependent on an adequate supply of thyroid hormones. Thus, iodine is an essential micronutrient for normal intellectual development and functioning.

T4 and T3, when released by the thyroid gland into the blood circulation, are predominantly bound to binding proteins. The unbound hormones, once released, enter the cells throughout the body where their ultimate metabolic impact is chiefly regulated by the type and activity of several deiodinase enzymes found within the cells. Certain tissue cells actively convert T4 to T3 while others predominantly convert T4 to an inactive isomer of T3, reverse triiodothyronine (rT3). More peripheral tissues like liver, kidney, and muscles obtain T3 directly from the blood T3, while the pituitary and other brain cells derive most of their cellular T3 from blood T4. Once within the cell, T3 becomes biologically active through binding to the nuclear T3 receptors, where it regulates growth, development, and specialization [2].

The iodine-replete pregnant woman is normally able to make available a ready supply of T4 to the devel-

oping fetus by transferring T4 through the placenta. The availability of T4 is enhanced during pregnancy through increases in binding proteins and the deiodinase enzyme system that favors the transfer of free T4 over free T3 to the fetus. It is of interest that new fetal tissue has a form of tissue deiodinase that converts the free T4 to intracellular active T3 rather than reverse T3. When the nuclear T3 receptors become more highly occupied, they promote more active cellular growth and development. This system is also more activated in the brain than in other tissues. After the major part of brain development has taken place, these systems become less active [5].

When people are iodine deficient, their circulating levels of T4 decline while the blood levels of T3 actually increase. This has several important consequences. Peripheral tissues, which rely predominantly on circulating T3 rather than T4, are relatively spared from the consequences of iodine deficiency, so the affected individuals appear as if they have normal thyroid status, and they grow relatively normally. On the other hand, the brain at the same time receives multiple insults from thyroid hormone deficiency. First, the maternal T4 supply is limited so the fetal brain does not develop normally. Second, because of the short supply of iodine from the mother to the fetus, when the fetus starts to develop its own thyroid hormone supply during the second trimester it also makes predominantly T3 rather than T4.

Endemic cretinism, arising from severe dietary iodine deficiency, is the most severe manifestation of maternal and fetal thyroid hormone deficiency. The hallmarks of endemic cretinism include mental retardation and a brain disorder. These symptoms are best described as spastic (pyramidal) signs in the upper limb distribution and rigidity (extrapyramidal) signs. These subjects have a diagnostic gait, which is not only related to the neurologic disorder, but also contributed to by joint laxity and deformity. Other frequently encountered clinical features include squinting, deafness, and primitive brain reflexes. In some populations there is the additional manifestation of endemic cretinism resulting from continuing thyroid hormone deficiency early in life. This results in additional clinical features of hypothyroidism: severe stunting of growth, skeletal retardation, and sexual immaturity. A prevalence of cretinism from 3% to 15% was commonly found in severely affected rural populations in many places around the world [3].

Iodine nutrition moves onto the stage

Although the benefits of iodized salt have been suggested since its introduction during the 1920s, options for programs to address iodine deficiency during the 1970s still involved a selection among various approaches. The urgency and extent of the problem were yet to become evident. In the past 25 years, a more realistic understanding of the nature and magnitude of the problem has emerged. Hetzel [6] introduced the term "iodine deficiency disorders" (IDD) in 1983 to encompass the broad range of the various clinical manifestations, including fetal damage and loss, endemic cretinism, impaired mental function, as well as goiter. This concept helped public policymakers to understand the broad extent of the dangers and aided in elevating a discussion of the problem on the agenda of governments and development agencies.

The damage from iodine deficiency in a society soon was shown to extend beyond the burden of people affected by the various clinical syndromes. A series of studies prior to the early 1990s comparing groups of apparently healthy people in iodine-deficient areas with those from neighboring areas and from groups where iodine deficiency was being corrected, showed a reduction of the entire distribution of cognitive ability in the deficient population by as much as 10 to 15 intelligence quotient (IQ) points [7]. Ultimately, the realization of the nature of the public nutrition problem arose from evidence that all members of an iodine-deficient population are affected even if the burden on the individual is not perceived or clinically demonstrable [8]. Covertly, iodine deficiency saps the cognitive performance and the productivity of humans and undermines their reproduction and survival. By using the term "hidden hunger," the late executive director of the United Nations Children's Fund (UNICEF), James P. Grant, voiced the new understanding: "Like the iceberg, its bulk lies beneath the surface" [9].

By 1990, iodine deficiency was documented in 118 countries with more than 1.5 billion people—more than one-third of the world's population, living in iodine-deficient areas [10]. It now has become evident that this was an underestimate. Improved criteria for population indicators of iodine deficiency [11] showed the real extent in, for instance, China [12], thus adding 800 million people to the global total. Also, data on iodine deficiency in the former USSR were not easily available at that time and subsequent information showed that the populations in the newly Independent States were iodine deficient, adding a further 250 million people to the global total [13, 14]. There is no exact calculation of what proportion of the world's populations at the start of the decade had a diet with insufficient iodine, but it would be realistic to estimate that between half and three-quarters of the world's population were affected.

Policy formulation to programs

The history of progress toward global elimination of iodine deficiency, from the age of ignorance, through

a half century of discovery, and to a decade of action, provides the insight that different elements of society had to learn to work together in new ways to tackle the problem through mutually supportive actions.

Member states at the World Health Assembly in May 1990 urged that the elimination of iodine deficiency be given priority nationally. Political commitment to the issue was made at the World Summit for Children in September 1990 at the United Nations (UN) when the virtual elimination of IDD was among 27 health and social development goals for the decade of the 1990s [15]. In 1991, a policy conference on hidden hunger translated the political goal into realistic policy guidelines and in 1992, the International Conference on Nutrition agreed upon a framework of action that would be incorporated in national plans.

Policy decision makers and other leaders were slow to recognize the nature and magnitude of problems arising from iodine deficiency, as well as to acknowledge that addressing the deficiency would require more than a mere Ministry-of-Health-led intervention. By the start of the 1990s, UNICEF, the World Health Organization (WHO), and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) had all argued for a multi-sectoral approach, but inter-agency agreement on guidelines for collaboration and standards of conduct in engaging the private sector needed sorting out. National and international coalitions for blending the public- and private-sector interests were needed. The experience of how to foster and manage these coalitions, however, was limited.

Meanwhile, many studies had documented the efficacy of appropriate daily delivery of iodine through common salt [16]. This set the stage for WHO and UNICEF to agree upon the strategy of universal salt iodization (USI) [17] as the prime method to be promoted and supported through their global networks. UNICEF amplified its commitment through a variety of approaches including support to national advocacy, procurement of equipment and supplies, technical assistance, and training.

To acquire evidence of national political and other commitments, national advocacy events of various kinds were organized. In South Asia, India's Prime Minister initiated a national discussion on the need for USI, and His Majesty the King of Bhutan decreed the need for iodized salt in the small nation. In Bolivia, UNICEF and the government arranged a meeting of members of the Cabinet to outline roles each Ministry played in national elimination programs, including key representatives of the productive sector. In the Philippines, the President chaired a meeting in the Malacannang Palace where the Secretaries of Education, Trade, Agriculture, Health, and others outlined sectoral commitments in the presence of producers, food processors, and the public.

To accentuate the point that "universal" meant all food-grade salt in all of the country, the Government of the People's Republic of China, supported by UNICEF and UNDP and with participation of ICCIDD, the Micronutrient Initiative (MI), the Program Against Micronutrient Malnutrition (PAMM), WHO, and the World Bank, held a meeting in 1993 of governors from all provinces and key national ministries at the Great Hall of the People [18] and declared national commitment to USI as the strategy for virtual elimination of IDD. The government then moved to borrow US $29 million from the World Bank to modernize the salt industry, a key factor for the successful household utilization rate in China today [19]. Similar national "dialogues" were held in the Republic of Georgia, Mongolia, Indonesia, Zimbabwe, Thailand, Pakistan, Russian Federation, Botswana, and Bangladesh.

Experience of these national policy events shows that forging the alliances needed to seek mutual agreement on a range of factors in national diligence—from general standards of quality and conduct to specific quality assurance needs—assured access to raw materials, fair market prices, internal and external monitoring systems, key components of a national communication strategy, appropriate legislative and regulatory processes, overriding political will, and sustained public demand for improved iodine nutrition.

To accelerate and support the emerging international and national efforts, development agencies of donor countries such as Australia, Belgium, Canada, Germany, Japan, the Netherlands, Sweden, and United States adjusted their allocation and technical assistance procedures to the budding new realities. In convincing donors, such as governments and other national leaders, that the solution was feasible, it was important to assure consistency of the policy message by evidence that the agreed-upon strategy leads to success. ICCIDD had been created in part to pull the many scientific opinions together as a forum for resolution hitherto not available to agencies and governments. The UN Sub-Committee on Nutrition provided a platform for development agencies to exchange views and experiences that supported IDD elimination. Nongovernmental technical organizations, such as ICCIDD, MI, and PAMM, provided expertise, expanded the number of trained professionals in many countries, and assisted in advocacy activities. To this was added the solid support of a civic group, Kiwanis International, as it undertook its first-ever international service project and agreed to raise US $75 million to eliminate iodine deficiency and to channel those resources through UNICEF to national endeavors.

After the initial government-led and public sector–dominated meetings that focused on elimination of IDD, an archetype change began to occur in the mid-1990s based on the recognition that neither the agencies nor governments owned, produced, or sold salt.

The "industry of salt" was the domain of the private salt producers and their allies. Notwithstanding their commitment to sound business and trade practices, it was crucial that salt producers grasped their central role for the successful elimination of iodine deficiency [20]. Part of coming to terms with this fact for public health officials was their recognition that a salt situation assessment and market-based salt supply analysis were as essential for national program direction as a survey of biologic status of the population. Salt producers needed to become a focus in any discussions that were seriously considering how to tackle the problem of iodine deficiency right from the start.

It has been estimated that during the last decade, the combined public sector investment in eliminating iodine deficiency was US $100 million while private investment was over US $1 billion [21]. Throughout the world, salt iodization has provided a trigger for upgrading and modernizing an industry that was operated on traditional lines. This has led to significant improvement in quality, hygiene, packaging and presentation of the product to the consumer.

Setting standards

WHO, in collaboration with ICCIDD and UNICEF, regularly reviewed IDD indicators and published improved standards [11, 22], which permitted a more accurate definition of the damage from iodine deficiency in the population, using biologic as well as clinical evidence. Also, recommended criteria to assess the national progress toward sustained elimination were discussed and published [23]. In addition to the assessment criteria, recommended levels of iodization [24] were considered and potassium iodate has been agreed upon as safe [25] and the most appropriate additive.

While the production of iodized salt increased rapidly in a variety of sites in many countries, the regulated levels of iodization were not derived from rigorous experiments. The initial calculations came mostly from salt consumption estimates, combined with the experience in countries like Switzerland and the United States, where voluntary iodization had been practiced since the 1920s. National officials often set the standards on the advice of international consultants and national advisors. Advice from salt experts and producers began slowly to be perceived as required. The levels of salt iodization observed at the midpoint of the decade of action varied as widely as from 15 to 100 mg iodine per kg of salt.

At the mid decade, a review of practices revealed that in some countries batches of iodized salt were reaching the market with varying levels of iodine content, in some instances of more than several times the permitted level. The appearance of an increased rate of thyrotoxicosis in Zimbabwe [26] led to national reviews in seven countries of Africa, coordinated by ICCIDD, UNICEF, and WHO [27], based upon which adjustments of recommended iodization levels were introduced [24].

In China, an additional problem arose when readily available iodized oil capsules containing milligrams rather than micrograms of iodine were promoted to schoolchildren for daily use. Others promoted iodized tea, iodized eggs, and other iodine-fortified products, causing an excess intake of iodine in some individuals. To sell these other products, entrepreneurs took advantage of the government-sponsored public information efforts in promoting the use of iodized salt.

From uncovering such issues, it became more evident that quality assurance and regular oversight were vital but underapplied components of many national management systems. Improved quality assurance plans were gradually introduced with more attention to the three domains of quality assurance, namely the essential product, the national process, and the progress in human nutrition (see box 1). Many of the practices indicated have been partly addressed, but more comprehensive monitoring efforts within production sites by salt producers and external monitoring by government services remain a significant challenge in many places.

Tracking progress

Information on the global progress being made toward the elimination of iodine deficiency has been gathered and published gradually, such as UNICEF's annual State of the World's Children Report. At first, the goiter prevalence was a key indicator [11]. Then, based on a 1999 recommendation by a joint expert consultation among ICCIDD, UNICEF, and WHO [22], the total goiter rate was no longer included because goiters do not totally regress as rapidly in populations that were

BOX 1. Three domains of quality assurance		
Essential product	National process	Progress in human nutrition
raw material processing packaging testing shipping retailing	tax incentives education communication management training laboratories political commitment legislation enforcement of standards inter-sectoral collaboration	periodic monitoring of iodine excretion public reporting of results application of new techniques

iodine deficient, even though urinary iodine levels increased to normal levels with the consumption of iodized salt [28–30]. To track progress, emphasis has now been put on the access and use in households of appropriately iodized salt.

In 1995, UNICEF reported that 58 out of 94 countries had achieved or were progressing well toward USI [31]. From 1995 onward, Multiple Indicator Cluster Surveys (MICS) were undertaken in countries, with assistance of UNICEF and other support groups. Using population proportional cluster sampling techniques, household surveys have been completed in more than 70 countries during the first round until 1997, and verbal questions were included about the consumption of iodized salt. At the end of the decade, the second round of national surveys to determine the progress toward reaching the World Summit on Children goals included iodine testing of salt found in households by a rapid screening kit. Where a MICS shows evidence that 90% percent of households have iodized salt, a national survey is recommended, including urinary iodine measurements, to verify that the national goal of virtual elimination of iodine deficiency has been achieved. Many countries have yet to act on this recommendation, but in some countries (e.g., Panama, Zimbabwe, Macedonia, and Bhutan) this success has now been documented.

The current situation

Figure 1 provides a summary of household availability of iodized salt by global region by 2000, collated by UNICEF [32]. More than 70% of households in the world used iodized salt by 1999, compared with less than 20% in 1990. By the end of the decade, iodized salt was found in over 90% of the households of 31 developing nations. In an additional 36 nations, more than half of the population was protected from iodine deficiency by consuming iodized salt. Large and populous countries as well as poorer countries are on these lists. Bangladesh, Benin, Bolivia, China, Eritrea, Nigeria, and Peru are among the examples of nations with solid successes in USI during the 1990s. This information comes from official government data received by the UN agency responsible. The apparent trends of increasing the percentage of households that have iodized salt during the decade in so many countries illustrate that once the USI policy had been communicated and the salt industry engaged, progress in country after country toward universal salt iodization accelerated.
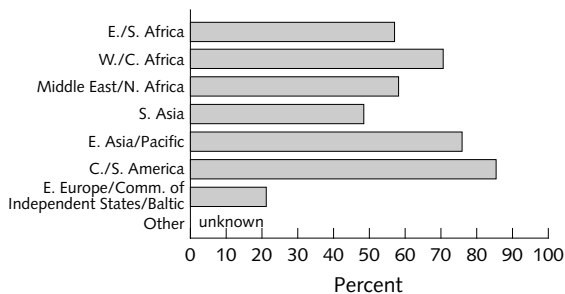
Figure 2 shows the estimated number of newborns protected by iodized household salt and the proportion not protected each year. It is estimated that at least 85 million newborns out of approximately 130 million annual births are protected every year from a loss in learning ability that might otherwise have occurred. This endows some three-quarters of a billion additional IQ points to the new generations of babies each year, helping them come closer to achieving their genetic intellectual potential and allowing them to attain higher educational and social development ambitions. Validation of national impact, through improved levels of urinary iodine, at this time has not yet been published from many countries. Where such data have been collected there is good accord between the percentage of availability of iodized salt in homes and the distribution of urinary iodine levels in the population, thus showing protection from iodine deficiency.

The Summit goal was not reached by 2000, however. While the global progress has been impressive, and some of the world's poorest nations have achieved high salt iodization levels, in 38 countries less than half of the population had access to iodized salt by the end of the decade. The list includes many countries of the Commonwealth of Independent States and East and Central Europe, where salt iodization practices once deemed adequate were abandoned in the transition and iodine deficiency returned with all the serious consequences for the future development of these populations.

FIG. 1. Estimated percentage of households with iodized salt by UNICEF regions in 2000
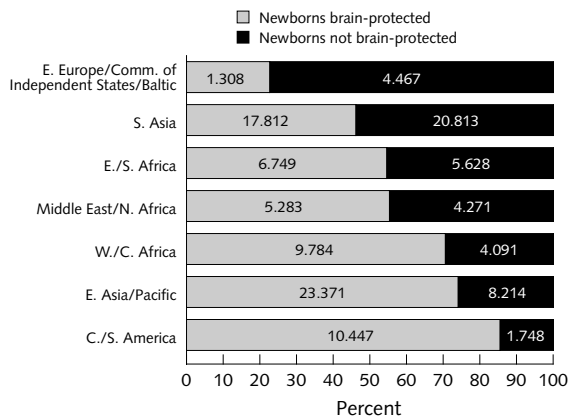

FIG. 2. Estimated number (millions) of newborns brain-protected each year, based on the percent of household availability of iodized salt, by UNICEF regions

Lessons learned

A barrier that has largely been overcome is the acceptance of food-grade salt as the vehicle for delivering additional iodine to populations. In some western countries, a few in the scientific and lay circles continue to discuss whether the customary salt intake is healthy [33]. On the other hand, consumers almost everywhere have accepted salt as a flavorful ingredient of common diets. Some expert advisors did not favor the USI strategy, even if it only substituted non-iodized for iodized salt, out of fear that its promotion would cause an increase in salt consumption. To date, there is no evidence that the promotion of salt iodization has caused consumption of more salt. Levels of iodization can be easily adjusted for any level of salt consumption.

An argument heard early in the decade that processed salt would not reach many people, especially those of poor and distant communities, revealed lack of understanding how the salt trade works. USI was perceived as beneficial for mostly urban areas and residents near main roads and upscale markets. Bolivia, Bhutan, Eritrea, Laos, and Nepal offer examples to the contrary. USI exerted its benefit also in the poorest and remotest rural areas, because almost all common grades of consumption salt can be iodized.

The successes of USI in country upon country are based on mutually supportive actions taken by concerned people from public-, private-, and civic-sector origins. It is not likely that any of the individual sectors alone could have achieved so much and so rapidly. The major lesson from the success of the decade was the recognition that the public- and private-sector abilities in overcoming iodine deficiency needed cohesive blending. A related lesson was that iodine deficiency was a *national problem*, not a local one, and that the approach should be *universal*, meaning addressing the entire population of the nation. After the demonstration that iodized salt is safe and that the processing technique is easy, the idea of "universal" salt iodization as the essential strategy became clear. The rapid, massive gains in household access to iodized salt would not have occurred through voluntary iodization of salt. With such an approach, the producer who decides to bear the extra work and expense of supplying iodized salt is unprotected in the market from his competitor who does not respond to the public health need of the nation.

During the final years of the decade, key international organizations involved in the global elimination of iodine deficiency strengthened their collaboration by forming a loose alliance. The shared goals of this alliance included the following: consolidating the gains already made in USI; stating more explicitly the special responsibility of salt producers; and jointly celebrating success while expanding the alliance into the future. To pursue these goals, regional salt producers' meetings were held in several parts of the world. The concerns and interests of salt industry participants were the main focus of discourse at these meetings, and governments and other partners were invited to ask the producers how they could help them with their efforts. This was a role reversal of what took place at the beginning of the decade. The climax from this change of approach occurred at the 8th World Salt Symposium, held on 7–11 May 2000 in The Hague, the Netherlands. The Symposium with the theme "Salt: Life Depends on It" featured the consolidation of progress and the need for continued commitment to USI in plenary and forum sessions, and in social and cultural events. The meeting attracted more than 1,000 participants involved with the salt industry and elimination of iodine deficiency from around the world [34].

At the symposium, a high-level roundtable meeting was held among the leaders from public, private, civic, and scientific organizations and steps were taken in support of the goal to expand on the mutually supportive work of the alliance in the future. Among the understandings reached was that the salt industry would take a more dynamic leading role in working to sustain the virtual elimination of iodine deficiency. Also, the collaboration of the key partnering organizations would be formalized and strengthened.

Future challenges

Dr. Gro Harlem Brundtland, Director-General of the World Health Organization, said at the 1999 World Health Assembly: "When the elimination of iodine deficiency disorders is achieved, it will be a major and total public health triumph, ranking even with small pox and poliomyelitis"[35]. Political decision makers are constantly changing, as are the issues that command their attention. Experience over the years in Thailand, Guatemala, Colombia, Germany, and countries from the former USSR illustrate that the iodine nutrition status of populations can quickly deteriorate when salt is no longer iodized after a period of adequate iodine nutrition. The need for sustained vigilance is illustrated by recent developments in India, where the political commitment to universal salt iodization is being tested. The salt situation, program status, and population iodine adequacy needs to be regularly assessed; and political will, along with other critical program elements, needs to be periodically renewed to assure continued adequate iodine nutrition.

More and more nations of the world are in a transition from a campaign mode (to reach the goal of USI) to activities (which ensure that the national successes are sustained). In simple terms, sustained elimination means that every family table and each processed food product containing salt always has salt with the appropriate quantity of iodine. The challenge of today

is to proceed permanently while assuring that what is achieved will be permanent. The actions for sustaining success may differ from the actions required to pursue it. Further research is needed to analyze the requirements that will assure continued positive results from the agreed upon USI policy.

Reports from Germany [36], Belgium [37], New Zealand [38], Australia [39], United States [40], France [41], and Italy [42] indicate the recent recognition that the iodine intake in economically advanced parts of the world has dramatically dropped or become deficient during the same period that most developing nations have been tackling their iodine deficiency problems. Scientists in these countries are now calling for closer monitoring and, in some cases, renewed policy action to prevent iodine deficiency through salt iodization. The time may have come to consider and accept the full global application of "USI forever."

In May 2002 members of the UN met in a Special Session on Children to review the score card of success in achieving the goals set out in 1990 and to make renewed commitments to protect women and children in the new millennium [43]. It was agreed that each country will report to the UN in 2003 on their progress toward the sustained elimination of iodine deficiency; the new global elimination target has been moved to 2005.

Although iodine deficiency was not eliminated as quickly as planned in the decade of the 1990s, the assembled leaders can be pleased with the progress made in most countries. A new Network for Sustained Elimination of Iodine Deficiency among the public-private-civic sectors was formally announced to advance this goal for the future and protect the gains already made [44]. The Network's establishment resulted from a process initiated by the high-level political leaders at Salt2000, who expressed that the effect of joint action by the talents of public, private, and civic sources in eliminating iodine deficiency is greater than the sum of its parts. This political wisdom will be needed when the issues of sustained iodine nutrition are addressed.

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Iron deficiency: Global prevalence and consequences

Rebecca J. Stoltzfus

Abstract

Iron deficiency is considered to be one of most prevalent forms of malnutrition, yet there has been a lack of consensus about the nature and magnitude of the health consequences of iron deficiency in populations. This paper presents new estimates of the public health importance of iron-deficiency anemia (IDA), which were made as part of the Global Burden of Disease (GBD) 2000 project. Iron deficiency is considered to contribute to death and disability as a risk factor for maternal and perinatal mortality, and also through its direct contributions to cognitive impairment, decreased work productivity, and death from severe anemia. Based on meta-analysis of observational studies, mortality risk estimates for maternal and perinatal mortality are calculated as the decreased risk in mortality for each 1 g/dl increase in mean pregnancy hemoglobin concentration. On average, globally, 50% of the anemia is assumed to be attributable to iron deficiency. Globally, iron deficiency ranks number 9 among 26 risk factors included in the GBD 2000, and accounts for 841,000 deaths and 35,057,000 disability-adjusted life years lost. Africa and parts of Asia bear 71% of the global mortality burden and 65% of the disability-adjusted life years lost, whereas North America bears 1.4% of the global burden. There is an urgent need to develop effective and sustainable interventions to control iron-deficiency anemia. This will likely not be achieved without substantial involvement of the private sector.

Key words: Anemia, iron deficiency, maternal mortality, perinatal mortality

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Introduction

Iron deficiency has long been considered a major form of malnutrition throughout the world, yet there has been a lack of consensus about the nature of the public health consequences of this widespread deficiency and which population groups deserve primary attention in terms of intervention [1]. However, many experts agree that in poverty-stricken populations, iron deficiency is not being adequately controlled by public health and nutrition interventions as they are currently implemented [2].

This paper presents new estimates of the public health importance of iron deficiency [3], with some implications for where resources might best be focused, both in terms of research and interventions. These estimates were made as part of the latest round of the World Health Organization's (WHO) Global Burden of Disease 2000 project (GBD 2000). Summary estimates have been published [4] and full reports are forthcoming.

Iron deficiency: results from GBD 2000

Within GBD 2000, iron deficiency was considered as one of several forms of malnutrition. For a detailed description of the methods and results, please see Stoltzfus et al. [3]. What follows here is a brief summary.

Conceptually, malnutrition—in this case iron deficiency—may cause death or disability either directly (i.e., direct sequelae) or by increasing the risk of death or disability from other causes (i.e., as a risk factor). For example, IDA directly causes impaired muscle function and physical performance [5], but it acts as a risk factor for maternal mortality. That is, women do not die in childbirth from IDA; rather, IDA increases a woman's risk of dying from cardiac failure in childbirth.

Iron deficiency was considered to potentially contribute to death and disability through the following outcomes: child mortality, maternal mortality, peri-

natal mortality, fitness and productivity, cognitive impairment, and morbidity from infectious disease. Of these, infectious morbidity was subsequently dropped, because the substantial epidemiologic evidence available does not support a significant relationship between iron deficiency and incidence or severity of infectious disease [6]. For child mortality there was insufficient epidemiologic data to provide sound estimates for IDA as a risk factor. This is a significant lack in the literature, and it is important to realize that the evidence does not preclude an important relationship.

To derive the risk estimates for maternal and perinatal mortality, hemoglobin concentration was used as the risk factor because there are insufficient studies (indeed, for maternal mortality, *no* studies) that measure IDA specifically as the risk factor. It was then assumed that 50% of anemia was attributable to iron deficiency. A further assumption was that the risk relationship between mortality and all anemia was the same as the risk relationship between mortality and the iron deficiency component of the anemia.

Population figures and anemia prevalence data were provided by the WHO, and are shown for the world and selected developing regions of the world in table 1. Anemia prevalence is highest in young children, followed by women. Data for other population groups are not shown here but are available in Stoltzfus et al. [3].

Mortality-risk estimates associated with pregnancy hemoglobin levels were derived from meta-analysis of 6 published studies of maternal mortality and 10 published studies of perinatal mortality. For both outcomes, the studies included in the analysis varied in their geographic location and included populations with and without endemic malaria. For perinatal mortality, there was evidence that the risk relationship was stronger in African studies than in studies from other locations, and, therefore, an Africa-specific risk estimate was used. Data from two recent studies were used to estimate the likely magnitude of bias in the summary estimates due to unmeasured factors. Based on this analysis, the risk estimates were attenuated by 20%. The final risk estimates are shown in table 2.

The GBD 2000 uses the disability-adjusted life year (DALY) as the summary measure of death and disability. The DALY measures years of life spent in less than full health. In the case of premature mortality, a full DALY is lost for each of year of expected life lost. For other disease states, a fraction of a DALY (i.e., disability weight) is assigned to each year lived with the disease, with the weight corresponding to the severity of the disease. In the case of IDA, premature mortality of mothers and children is one source of DALYs lost. Another is the disability weight assessed as a fraction of a DALY for each year lived with anemia or its associated cognitive and physical impairment.

Globally, 841,000 deaths and 35,057,000 DALYs are attributable to IDA (table 1). The relationship between

Table 2. Odds ratios and confidence limits used to generate GBD 2000 mortality estimates

Outcome	Estimate	95% C.I.
Maternal mortality	0.80	0.70 – 0.91
Perinatal mortality, Africa	0.72	0.65 – 0.80
Perinatal mortality, other regions	0.84	0.78 – 0.90

Source: Stoltzfus et al. [3]

Table 1. Population, anemia prevalence in risk groups, and death and disability attributable to iron-deficiency anemia in the world and in selected developing regions of the world

Region	Population (thousands)	Anemia prevalence			Burden attributable to iron deficiency (thousands)	
		Women	Men	Children	Deaths	DALYs[a]
Africa[b]	639,593	41%	28%	60%	271	10,140
Latin America[c]	502,162	23%	11%	46%	33	1,249
Eastern Mediterranean[d]	481,635	44%	17%	63%	80	3,195
Southeast Asia-I[e]	293,819	49%	32%	49%	34	1,528
Southeast Asia-II[f]	1,241,806	60%	36%	66%	324	12,497
North America[g]	325,183	8%	5%[h]	7%	5	478
World	6,045,017	—		—	841	35,057

Source: Stoltzfus et al. [3]
a. DALY = disability-adjusted life year
b. Excluding Egypt, Morocco, Somalia, Sudan and Tunisia.
c. Excluding Cuba
d. Afghanistan, Djibouti, Egypt, Iraq, Morocco, Pakistan, Somalia, Sudan, Yemen
e. Indonesia, Sri Lanka, Thailand (I)
f. Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Maldives, Myanmar, Nepal (II)
g. Including Cuba
h. Because anemia cutoffs are defined as the 5th percentile of a normative distribution, this represents the theoretical minimum population prevalence of anemia

maternal pregnancy anemia and perinatal mortality is responsible for the largest contribution to both deaths and DALYs, representing 56% of the total [3, 4].

The global distribution of the disease burden of IDA is heavily concentrated in Africa and WHO region Southeast Asia-D (table 1). These regions bear 71% of the global mortality burden and 65% of the DALYs lost. By contrast, the DALYs lost to IDA in North America and Cuba amount to 1.4% of the global total. It is an important (but not surprising) message that there is enormous inequity in the burden of iron deficiency in the world. There is an equally enormous need for interventions that will work in the less-developed regions of the world.

Another interesting comparison between world regions is the relative importance of maternal and perinatal mortality, which derives entirely from pregnancy anemia, compared with the "direct consequences" of iron deficiency, which derive primarily from childhood IDA. This is shown graphically in figure 1. It is important to remember that the relative sizes of these regional "pies" are vastly different. In fact, if these pies were truly proportional in size, the pie representing North America and Cuba would be barely visible, at about 5% of the total pie for Africa. (Exact ratios can be calculated from table 1.) Nonetheless, these pie graphs demonstrate that the relative importance of the different consequences of IDA varies by context. In regions where mortality rates are high, pregnancy anemia rates are also almost invariably high, and these two combine to create very large burdens of perinatal and maternal mortality attributable to IDA during pregnancy. In Africa, 81% of the total DALYs derives from mortality

associated with pregnancy anemia. This fraction is also high in Latin America (61%), Eastern Mediterranean-D (72%), and Southeast Asia-D (68%) (see table 1 for regional definitions). By contrast, in North America and Cuba, only 10% of total DALYs derives from pregnancy anemia, with the remaining 90% coming from the direct disabling sequelae of IDA. The same is true for European countries with very low mortality rates (data not shown). The resulting message is that as overall mortality rates decline, the relative importance of the direct sequelae (i.e., cognitive impairment and decreased work productivity) increases, while that of pregnancy anemia and its associated mortality decreases.

It is an important caveat that the GBD 2000 project likely underestimates the consequences of IDA in childhood for two important reasons. First, as stated above, data are lacking to estimate the risk relationship between IDA and childhood mortality, even though a true relationship might exist. Second, the DALY, being a measure of disease and disability, does not capture fully the developmental consequences of IDA in childhood, which mainly involve changes in function within the range of "normality." That is, IDA is associated with shifts in intelligence that mainly fall within the range of normal function, rather than clinical retardation. Economic measures of the consequences of IDA would tend to weight the effects of IDA on cognition and work productivity much more heavily than its effects on maternal and perinatal mortality [7]. Thus, it is extremely important to understand the measuring stick used in the GBD 2000. It is a measure of health consequences and only health consequences.
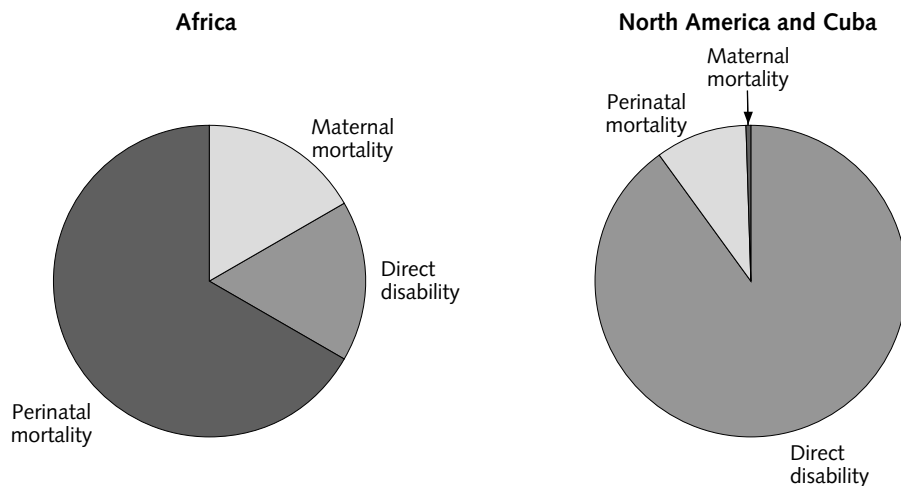
FIG 1. Proportions of DALY's attributable to mortality and disability in Africa and North America and Cuba. The relative contributions of perinatal mortality, maternal mortality, and direct disability (i.e., cognitive impairment and decreased work productivity) to the total disability-adjusted life years (DALYs) lost to iron-deficiency anemia in two regions of the world, Africa vs North America and Cuba. In Africa, maternal mortality contributes 15% of DALYs lost, perinatal mortality contributes 66%, and direct disability contributes 19%. In North America and Cuba, maternal mortality contributes < 1% of DALYs lost, perinatal mortality contributes almost 10%, and direct disability contributes almost 90%. Source of data: Stoltzfus et al. [3]

Implications and conclusions

GBD 2000 estimates provide a new basis for advocating the control of iron deficiency. Compared with other forms of malnutrition included among the 26 risk factors in GBD 2000 (table 3), iron deficiency ranks #9 overall in terms of DALYs lost, falling lower than underweight (#1), and slightly higher than zinc deficiency (#11) and vitamin A deficiency (#13). There is no excuse for the scientific and public health community to be complacent about iron deficiency.

At the same time, GBD 2000 further illuminates important gaps in our knowledge about the consequences of iron deficiency. Evidence for the relationships between IDA and maternal and perinatal mortality needs to be strengthened by well-controlled prospective observational studies. Randomized trials are conceivable and would add greatly to the evidence base, but will likely not be placebo-controlled for ethical reasons. As previously mentioned, there is an urgent need for more evidence on the relationship between IDA and mortality in young children. Fortunately, research is in process to address this question.

Regarding the relationship of iron deficiency to child development, cognition, and work productivity, as described by Dr. Tomas Walter in the colloquium [8], evidence is mounting that early iron deficiency significantly affects children's neural physiology and behavior [5]. Well-controlled observational studies show that IDA is associated with behavioral differences, developmental delays, and lower IQ and poorer school performance [9]. Two published randomized controlled trials of iron supplementation in early childhood have

both shown benefits to children's development [10, 11]. There is a need for longitudinal studies of cohorts of children whose iron status in early childhood is well described, so that the long-term consequences of early deficits can be described in social, economic, and educational terms [12].

There is also a need for further research that describes the effects of IDA on people's well-being and activities in social terms. Iron deficiency adversely affects work productivity of adults, and likely also affects voluntary activities[13]. A particularly salient area for future research is the effect of maternal IDA on well-being and care-giving capacities and behaviors in the postpartum period. These effects are difficult to characterize because of the numerous methods of coping that humans use to adapt to compromised health. Yet the implications for the lives of women and infants may be significant, and these studies are certainly within the reach of innovative social scientists.

These gaps in the evidence should not preclude advocacy and action. It is striking that while iron deficiency in developed countries is being controlled mostly through private sector actions—namely availability of iron-rich foods and iron-fortified weaning foods—the public sector is shouldering the burden of iron interventions in less-developed countries, and frankly is failing. During the colloquium, Nita Dalmiya informed us that UNICEF is the largest distributor of iron supplements in the world [14]. This is an untenable solution to the problem. The question is not only one of sustainability, because at this point there is little or no success to be sustained. A recent WHO progress report on malnutrition [15] stated:

> "Unfortunately, there has been little appreciable change over the last two decades in the high worldwide prevalence of IDA. Few active programmes in both developed and developing countries have succeeded in reducing iron deficiency and anaemia. Important factors contributing to the lack of progress include failure to recognize the causes of iron deficiency and anaemia, lack of political commitment to control it, inadequate planning of control programmes, insufficient mobilization and training of health staff, and insufficient community involvement in solving the problem." (p. 17)

In the context of the industry-sponsored colloquium, two critical needs to address the burden of IDA were emphasized. First is the need for affordable, appealing products. Despite the high prevalence and large disability burden associated with early childhood anemia, affordable, high-quality, and appealing supplemental forms of iron designed for young children are generally not available in less-developed countries. Even UNICEF currently does not stock an iron supplement for young children. This has been a challenge because young children cannot safely swallow hard pills, and liquid supplements are bulky to ship and store and are relatively unstable chemically. Preparations designed to

Table 3. Relative rank and attributable DALYs for 13 risk factors considered in GBD 2000 [a,b]

Rank	Risk factor	Attributable DALY
1	Underweight	137,801
2	Unsafe sex	91,869
3	High blood pressure	64,270
4	Tobacco	59,081
5	Alcohol	58,323
6	Unsafe water, sanitation, and hygiene	54,158
7	High cholesterol	40,437
8	Indoor smoke from solid fuels	38,539
9	Iron deficiency	35,057
10	High body mass index	33,415
11	Zinc deficiency	28,034
12	Low fruit and vegetable intake	26,662
13	Vitamin A deficiency	26,638

Source: Ezzati et al., 2002 [4].

a. Shown here are the top 13 risk factors; those ranked 14–20 are (in order): physical inactivity, occupational risk factors for injury, lead exposure, illicit drugs, unsafe health-care injections, lack of contraception, childhood sexual abuse.

b. Global total: 1.46 billion

appeal to children also introduce the risk of toxic overdose, so issues of dose and packaging are critical from a safety standpoint. Innovations such as home fortificants [16] ("sprinkles"), spreads, "foodlets" [17], and powdered beverages like the one developed by Procter & Gamble Co. [18] are potential solutions, if they can be made widely available at affordable prices.

Second, the public sector working through clinical distribution channels can only achieve targeted periods of supplementation of short duration (e.g., prenatal care). While these approaches are needed to create a safety net during high-risk periods, they cannot control the problem completely. As has been the case with North America, there needs to be private sector involvement; i.e., the opportunity for people to purchase dietary iron supplements or iron-fortified foods for consumption in high-risk periods (e.g., early childhood and pregnancy) and as needed throughout the life cycle. The need for private sector provision of dietary iron supplements is perhaps even more acute where governments are in financial and political crisis, or where the public sector functions poorly. Unfortunately, this is true for many of the least developed regions where the burden of IDA is greatest.

Recent ethnographic work on women's perceptions of anemia and anemia treatments in Pemba Island, Zanzibar supports this argument. Young [19] concluded that over-the-counter pharmacies are among the most empowering places for Zanzibari women to receive health care. In the context of a poorly functioning public health care system, small private pharmacies provide an alternative to irregular supplies from a government perceived as oppressive, because customers have immediate access to iron pills and are "no longer patients without any real bargaining power, at the mercy of potentially hostile or indifferent staff" [19, p. 110]. Furthermore, private pharmacies are generally convenient, require less waiting, are not dependent on uncertain donor aid, and provide a living for the owners. They appear to be a win-win situation for both the small business owner and women seeking care.

There is an important role to be played by companies that manufacture pharmaceutical and food products to develop high-quality, appealing, safe products that can be distributed through local markets. Such work is urgently needed to reduce the burden of disability and death associated with the present high prevalence of IDA.

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Effect of iron-deficiency anemia on cognitive skills and neuromaturation in infancy and childhood

Tomas Walter

Abstract

Iron-deficiency anemia in infancy has been consistently shown to negatively influence performance in tests of psychomotor development. In most studies of short-term follow-up, lower scores did not improve with iron therapy, despite complete hematologic replenishment.

The negative impact on psychomotor development of iron-deficiency anemia (IDA) in infancy has been well documented in more than a dozen studies during the last two decades. Two studies will be presented here to further support this assertion. Additionally, we will present some data referring to longer follow-up at 5 and 10 years as well as data concerning recent descriptions of the neurologic derangements that may underlie these behavioral effects.

To evaluate whether these deficits may revert after long-term observation, a cohort of infants was re-evaluated at 5 and 10 years of age. Two studies have examined children aged 5 years who had anemia as infants using comparable tools of cognitive development showing persisting and consistent important disadvantages in those who were formerly anemic. These tests were better predictors of future achievement than psychomotor scores. These children were again examined at 10 years and showed lower school achievement and poorer fine-hand movements. Studies of neurologic maturation in a new cohort of infants aged 6 months included auditory brain stem responses and naptime 18-lead sleep studies. The central conduction time of the auditory brain stem responses was slower at 6, 12, and 18 months and at 4 years, despite iron therapy beginning at 6 months. During the sleep-wakefulness cycle, heart-rate variability—a developmental expression of the autonomic nervous system—was less mature in anemic infants. The proposed mechanisms are altered auditory-nerve and vagal-nerve myelination, respectively, as iron is required for normal myelin synthesis.

Key words: Iron deficiency, anemia, behavior, developmental neurology

Behavioral studies

When IDA ensues during the first 2 years of life, it is associated with delayed psychomotor development and changes in behavior. These effects have been shown to persist after several months of iron therapy, despite complete correction of iron nutrition measures. Moreover, it is still uncertain after an extended period of observation whether or to what extent these derangements are reversible. It is worrisome that the long-term prospective follow-up studies reported to date, to be discussed below, show the persistence of cognitive deficits at 5 to 6 and at 10 years of age in those who experienced IDA during infancy.

The inherent difficulties of identifying intervening variables in the complex field of mental development, coupled in some cases with suboptimal design, have prevented significant progress in the investigation of iron deficiency. However, two studies—one conducted in Costa Rica in 1982 [1], and the other in Santiago, Chile, in 1986 [2]—confirm conclusions arising from previous work.

The study in Santiago was performed in association with a field trial of fortified infant foods. A total of 196 healthy, full-term infants were assessed with the Bayley Scales of Infant Development (BSID) [3] at 12 (see Box 1), 12½, and 15 months of age. This well-known and accepted tool is used to determine psychomotor development from ages 3–42 months. It consists of a mental scale to evaluate cognitive skills, such as language acquisition and abstract thinking, and a motor or psychomotor scale to evaluate gross motor abilities, such as coordination, body balance, and

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Box 1. Bayley Scales of Infant Development

» Psychomotor development of the infant
» Mental development index (MDI)
» Psychomotor development index (PDI)
» Adjustment for the age 100 ± 16 (like the IQ)
» Behavior scale: psychologic evaluation

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walking. These scales are expressed as an index adjusted for age as the Mental Development Index (MDI) and the Psychomotor Development Index (PDI). In addition, it includes an Infant Behavior Record, which is based on clinical evaluation by a psychologist.

The Costa Rican study [1] enrolled 191 otherwise healthy 12- to 23-month-old infants with heterogeneous iron status. The infants were divided into groups ranging from most to least iron deficient. The Bayley's scales of infant development were administered before, after 1 week, and after 3 months of iron treatment with appropriate placebo controls. These infants were tested further after 6 months with unchanged results [4].

Results of psychomotor studies in infancy

Four major questions related to iron deficiency were answered with these studies and are discussed below.

At what stage of iron deficiency is infant behavior adversely affected?

It was clear in both studies that a decrease in hemoglobin below the conventional cutoff limit for anemia was necessary to significantly affect mental and psychomotor development scores. This has also been the case for most similar studies. The performance of the iron-deficient infants without anemia as a whole was indistinguishable from that of the iron-replete controls.

In the Chilean study [2] among anemic infants, hemoglobin (Hb) concentration was correlated with performance. The lower the Hb, the lower the developmental scores. Similarly, in the Costa Rican study, infants with moderate iron deficiency anemia (Hb < 100 g/L) had lower mental and motor test scores than appropriate controls. The Santiago study [2] also evaluated the effect of chronic anemia. Infants whose anemia had duration of 3 or more months had significantly lower mental and motor development indices than did those with anemia of shorter duration. The results of other research published to date support the conclusion of these two studies: iron deficiency severe and chronic enough to cause anemia is associated with impaired achievement in developmental tests in infancy, and as anemia becomes more severe [5], deficits are more profound [5–8].

Why is severe iron deficiency—enough to lead to anemia—necessary to affect behavior?

This is an unanswered question. Animal experimentation shows that brain iron is acquired early in postnatal life; has a very slow turnover and when an iron deficient diet is provided, the decrease in hemoglobin production coincides with the depletion of tissues [9–11]. Therefore, anemia may be a reflection of tissue iron depletion severe enough to somehow affect behavior. On the other hand, the behavior measures available for this age group might be insensitive to subtle changes that may be present before the progression to anemia.

Effect of iron treatment

Consistent results have been obtained in studies that have included a placebo treatment group. Together, these studies indicate that short-term increases in test scores observed among iron-treated anemic infants are not significantly greater than those among placebo-treated anemic infants, but are thus likely related to a practice effect.

Although separating the effects of iron deficiency without anemia from those of IDA is important, a more pertinent question from a clinical perspective is whether iron therapy completely corrects behavioral abnormalities regardless of how soon the changes are detectable. Studies in Costa Rica [1], Chile [2], the United Kingdom [12], and Indonesia [6] included an iron treatment period of 2 to 4 months after which psychomotor development tests were repeated. Despite improved iron status, most of the formerly anemic infants were unable to improve their psychomotor performances. The only study to date that showed a convincing reversal of lower BSID scores is the Indonesian study [6].

Notwithstanding, in most of the studies iron therapy, even complete iron repletion was ineffective in improving the psychomotor scores of anemic infants to the level of nonanemic controls. The protocol in Indonesia [6] shows that studies in this field may give conflicting results and that newer and more imaginative techniques must be used to elucidate current controversies.

Specific patterns of failure

The Chilean study [2] found that with regard to the mental scale, fewer anemic infants than control infants successfully completed tasks that required comprehension of language without visual demonstration. In the psychomotor scale balance in the standing position (sits from standing, stands alone, and stands up) and walking were accomplished by significantly fewer anemic infants than controls (see tables 1 and 2). Similar findings were reported in the Costa Rican study [1].

Information about other behavioral differences has been limited. Previous work relied primarily on rating scales during developmental testing, and most studies used the Bayley Scale's Infant Behavior

TABLE 1. Mental scale items (12 months)

| Description (item no.) | Infants passing (%) | | |
	Anemic	Control	*p* value
Pushes car along (99)	56	77	NS
Turns book pages (103)	69	83	NS
Imitates words (mama, dada) (106)			
At 12 months	13	47	0.01
At 15 months	75	100	0.07
Says two words with meaning (113)			
At 12 months	0	7	NS
At 15 months	42	93	0.005
Points own toys, shoes or clothing (117)			
At 12 months	0	18	NS
At 15 months	25	60	0.07

TABLE 2. Motor scale items (12 months)

| Description (item no.) | Infants passing (%) | | |
	Anemic	Control	*p* value
Walks with help (42)	85	97	NS
Sits from standing (43)	67	97	0.01
Pat-a-cake (44)	82	97	NS
Stands alone (45)	64	93	0.02
Walks alone (46)	38	67	0.05
Stands up from sitting (47)			
At 12 months	3	7	NS
At 15 months	42	80	0.05
Stands on left foot with help (52)			
At 12 months	0	10	NS
At 15 months	8	40	0.05

Record. Nonetheless, observations have suggested a pattern of alterations. Infants with IDA were rated as unusually fearful, tense, restless, hesitant, withdrawn, or unhappy during testing [13]. In addition, infants with iron deficiency without anemia have been rated as more "solemn" than infants with better iron status. The only study to examine behavior in a context other than developmental testing of infants with documented IDA was conducted by Lozoff and colleagues in Guatemala [14]. During a short free-play period, quantitative coding of behavior showed that iron-deficient anemic infants and their mothers maintained closer proximity to each other than did comparison group dyads. The authors postulated that the pattern of closer proximity reflected heightened attachment behavior, a counterpart of the fearfulness and hesitance noted on behavioral ratings during developmental testing and evidence of altered affect, activity, or energy.

The preventive trial in Chile

The children in this protocol participated in two studies that comprised a recent project [15]—a preventive trial. Study I, a clinical trial of the developmental effects of preventing IDA, involved 1700 healthy Chilean infants and their parents living in suburban areas near the capital city of Santiago. The infants, who were 4 to 5 months old and receiving well-child care in the designated community clinics, were screened for the following entrance criteria: residence in the targeted area, birth weight ≥ 3.0 kg, no major birth or neonatal complications, no jaundice requiring phototherapy, no hospitalization at any age, no iron-containing preparations at any age other than those given by the study, and no major acute or chronic illness.

Qualifying infants were randomly assigned to a high-iron or no-added-iron condition at 6 months of age. Infants who were already receiving more than 250 ml/day of unmodified cow's milk or formula were randomly assigned to iron-fortified formula or no-added-iron milk. Breast-fed babies consuming < 250 ml/day of cow's milk or formula were randomly assigned to receive vitamins with or without iron and once cow's milk was introduced, the formerly assigned type of milk. Prior to randomization, a venipuncture excluded the few who were anemic (Hb < 110 g/L plus two or more abnormal biochemical measures) from the preventive trial. Hematologic assessments at 12 months were performed on all participants. The main outcome variable to assess developmental status of all infants was the Bayley Scales of Infant Development at 12 months, in addition to a visual attention measure at 6 and 12 months, a temperament measure, and determination of the timing of motor milestones. Study II, consisting of neuromaturational evaluations, was done with the anemic infants at 6 or 12 months of age as below.

Because several studies have shown that the association between IDA in infancy and lower developmental test scores is confounded by environmental disadvantages, Study I of this project was a double-blind, placebo-controlled preventive trial in which healthy Chilean 6-month-old infants were randomly assigned to supplemental-iron or no-added-iron treatments until 12 months of age. At 12 months, the supplemented group had less anemia (Hb < 110 g/L) and less iron deficiency without anemia (two or three abnormal measures: free erythrocyte protoporphyrin (FEP), mean corpuscular volume (MCV), or serum ferritin (SF); however, in contrast to a recent smaller preventive trial in Canada [16], we could not show higher Bayley mental (MDI) or psychomotor (PDI) development index scores related to absence of anemia.

For Study I, healthy full-term Chilean infants who were free of iron-deficiency anemia at 6 months were
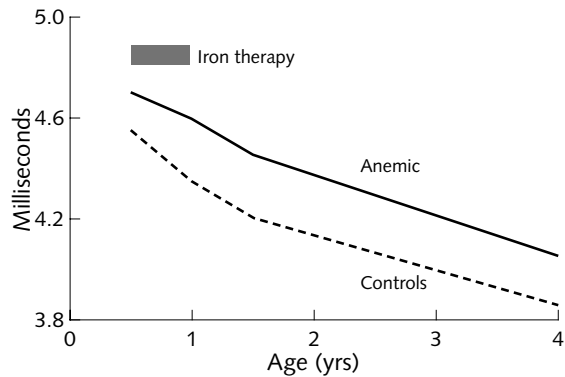
FIG. 1. Evoked auditory brain stem potentials (ABS) of the anemic and control children at 6 months and up to 4 years. The differences in speed of central conduction time in milliseconds are significant at all points ($p < 0.001$).

assigned to high- or low-iron groups or to high- or no-added-iron groups. Behavioral/developmental outcomes at 12 months of age included overall mental and motor test scores and specific measures of motor functioning, cognitive processing, and behavior. There were no differences between high- and low-iron groups in the prevalence of iron-deficiency anemia or behavioral/developmental outcome, and they were combined to form an iron-supplemented group ($n = 1123$) for comparison with the no-added-iron group ($n = 534$) At 12 months iron-deficiency anemia was present in 3.1% and 22.6% of the supplemented and unsupplemented groups, respectively. The groups differed in specific behavioral/developmental outcomes but not global test scores. Infants who did not receive supplemental iron processed information slower. They were less likely to show positive affect, interact socially, or check their caregivers' reactions. A smaller proportion of them resisted giving up toys and test materials, and more could not be soothed by words or objects when upset. They crawled somewhat later and were more likely to be tremulous. The results suggest that unsupplemented infants responded less positively to the physical and social environment. The observed differences appear congruent with current understanding of the effects of iron deficiency on the developing brain. The study shows that healthy full-term infants may receive developmental and behavioral benefits from iron supplementation in the first year of life.

Long term effects of iron-deficiency anemia on cognitive performance

The long-term effects of IDA have been addressed by two recently described follow-up studies in 5-year-old Costa Rican [17] and Chilean [18–20] children who had been well characterized as infants in both iron status environmental variables and psychomotor

development. These children were the subjects of respective reports during their infancy described above [1, 2]. At 5 years of age, an evaluation with a comprehensive set of psychometric tests showed that those who as infants had presented with IDA had lower scores on many of these tests when compared with children with higher hemoglobin in infancy. These disadvantages persisted after statistical control of many potentially confounding variables. At this age (5 years), measures of cognitive development are better predictors of future achievement, so they are even more reason for concern. For example, a 5-point drop in intellectual quotient (IQ) was consistent in both studies, as well as in other tests concerned with intellectual function. Five points of IQ are a significant handicap affecting millions of infants that have or have had anemia worldwide. This is worrisome because this is a preventable deficit.

Neuromaturation studies

IDA has long been thought to have central nervous system effects. However, finding direct evidence of such impact in the human infant has presented many methodological challenges. Auditory brainstem responses (ABR), which represent the progressive activation of the auditory pathway from acoustic nerve (wave I) to the lateral lemniscus in the brain stem (wave V), provide a non-invasive means of examining an aspect of the central nervous system that is rapidly maturing during the age period when iron deficiency is most common. Another rapidly maturing process in infancy is the balance of the autonomic nervous system. Experimental animals have also aided in orienting human studies.

Studies of ABR responses in infants with IDA

As part of Study II we studied auditory brain stem responses (ABR) during spontaneous naps in 55 healthy 6-month-old Chilean infants with IDA and 26 nonanemic controls [21, 22]. Central Conduction Time (CCT), the Wave I–IV interpeak latency, was longer in the iron-deficient anemic group, with differences becoming more pronounced at follow-up at 12 and 18 months, despite effective iron therapy, and continuing to be slower at a 4 years of age follow-up (fig. 1) [23–26]. The CCT is considered an index of central nervous system development, because myelination of nerve fibers and maturation of synaptic relays lead to an exponential reduction in CCT from birth reaching adult levels at 24 months. The pattern of resulting differences in latencies but not amplitudes, in longer CCT (as an overall measure of nerve conduction velocity) indicates that altered myelination is an appealing explanation, especially in view of recent laboratory work documenting iron's essential role in myelin formation and maintenance [27–31]. This study shows that IDA adversely affects at least one aspect of

central nervous system development in 6-month-old infants that lasts at least to 4 years of age and suggests the benefits of studying other processes that are rapidly myelinating during the first 2 years of life.

Sleep studies and autonomic nervous system development

Maturational patterns of heart rate variability (HRV) provide noninvasive tools for the investigation of central nervous integrity during early human development and are likely to reflect brain function alterations earlier and more closely than tests of behavior and psychomotor development. Patterns of heart rate and HRV were measured in 18 anemic 6-month-old infants and corresponding control infants from polygraphic recordings during quiet and active sleep and wakefulness [32, 33]. Iron-deficient anemic infants presented lower amplitude in all sleep-wake states. It was proposed that delayed myelination of the vagal nerve results in decreased parasympathetic influences that may underlie behavioral effects in iron deficiency in infancy.

Reliance on animal studies

The many challenges of studying the central nervous system in human infants has meant that direct evidence of central nervous system effects has had to come from animal studies. That evidence is increasingly compelling. In addition to earlier research on iron's role in central nervous system neurotransmitter function [34–38], recent work shows that brain iron is essential for normal myelination [27–31, 39, 40]. In rats, there is an influx of transferrin and iron into the brain in the immediate postnatal period. As iron and its transport and storage compounds are redistributed in the brain, myelinogenesis and iron uptake are at their peak. Iron and its related proteins concentrate in oligodendrocytes and become more concentrated in white than in gray matter (the majority of brain iron is found in this myelin fraction). Oligodendrocytes synthesize fatty acids and cholesterol for myelin production, a process that requires iron. Furthermore, animal studies have consistently found a lasting deficit in brain iron when IDA occurs early in development [9–11]. Although only two studies of iron deficiency in animal models examined myelination directly, both found iron-deficient rats to be hypomyelinated [29, 40].

Challenges in designing clinical studies

The results of these and other animal studies indicate that IDA during brain growth has long-lasting effects on the central nervous system. Yet obtaining evidence of similar effects in the human infant has posed many methodologic challenges. During the last 20 years, research on the effects of IDA and iron therapy on infant development has depended heavily on standardized tests of infant development, which have serious limitations and bear unknown relations to central nervous system functions. By measuring auditory-evoked potentials, we provide more direct evidence of central nervous system alterations in infants with IDA. Such neurophysiologic measurements had not been previously conducted in the iron-deficient infant.

Changes in auditory brainstem-evoked potentials or responses (ABRS) are particularly relevant to study in infants with IDA. ABRS consist of a succession of five to seven waves recorded at the scalp within the first 10 milliseconds after stimulation. Development changes in ABRS have been carefully studied. There are well-established developmental progressions from birth until stable values are reached at 18 to 24 months, with decreases in the absolute and interpeak latencies, decrease in duration, and increase in amplitude [21–23]. Latency changes have been related to increases in conduction velocity during axonal myelination. Other changes, such as increase in amplitude and reduction in duration, are probably due to improvements in synchronization at the axonal or synaptic levels. Thus, these developmental progressions are occurring during the age period when iron deficiency is most common.

Conclusions

Behavioral studies have consistently shown that IDA has adverse effects. Perhaps the most important implication of our findings, however, is that they may further generate plausible and testable hypotheses about the effects of iron deficiency on the developing central nervous system. Many parts of the brain are becoming myelinated in the first 2 years of life, when iron deficiency is most prevalent. We are obtaining more direct and indirect non-invasive measures of myelination in the human. With the hypothesis of impaired myelination in early IDA, it should be possible to design studies with specific measures, using techniques such as positron emission tomography (PET) scan imaging, evoked and spontaneous potentials, and, eventually, behavioral progressions known to depend on myelination. Such hypothesis-driven research would be a substantial advance over previous studies of iron-deficient infants, which has largely depended on global tests of development. Thus, these studies suggest new, promising directions for understanding more specific central nervous system mechanisms by which IDA could alter infant behavior and development.

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Multiple-micronutrient fortification technology development and evaluation: from lab to market

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Abstract

At the World Summit for Children (New York, 1990), a resolution was passed to eliminate vitamin A and iodine deficiencies and significantly reduce iron-deficiency anemia by the year 2000. In responding to this urgent call, we developed a unique multiple-micronutrient fortification delivery system called "GrowthPlus/ CreciPlus®." Using this technology, a fortified powder fruit drink has been formulated and extensively evaluated. One serving of the product delivers the following US recommended dietary allowances: 20–30% of iron; 10–35% of vitamin A; 25–35% of iodine; 100–120% of vitamin C; 25–35% of zinc; 15–35% of folate; and 10– 50% of vitamins E, B_2, B_6, and B_{12}. This was accomplished through (a) identifying and selecting the right fortificants, and (b) understanding their chemical and physical properties that contribute to multiple problems (product acceptability, stability, and bioavailability). Data from a home-use test showed fortification with the "Multiple-Fortification Technology" has no effect on the appearance and taste of the eventually consumed powder fruit drink. One-year stability studies demonstrated that iodine and the vitamins have adequate stability. Bioavailability evaluation by using double-isotope labeling technique showed that the iron from the fortified powder drink has excellent bioavailability (23.4% ± 6.7). In conclusion, a powder fruit drink has been clinically demonstrated to deliver multiple micronutrients, which include adequate levels of bioavailable iron, vitamin A, iodine, zinc, vitamin C, and B vitamins, without compromising taste, appearance, and bioavailability. The critical limiting step in the micronutrient fortification program is the production and distribution of the multiple-micronutrient-fortified product. The fortified powder drink was marketed in Venezuela under the brand name NutriStar®.

Key words: Fortification, iron bioavailability, micronutrients, powder fruit drink, vitamin stability

Introduction

More than 2 billion people worldwide suffer from iron, iodine, and vitamin A malnutrition [1–3]. When they are not prevented or remain untreated, such deficiencies have been shown to cause serious health and economic problems. These include stunted growth, impaired mental development, fatigue, poor school performance, increased morbidity and mortality, reduced work output, and low self-esteem. In all, micronutrient malnutrition is among the leading cause of poor public health and economic development [1–3]. That is why the phrase "hidden hunger" is used to describe the nature and seriousness of the deficiencies of these three micronutrients and why it is emerging as a top priority on the global public health agenda [1]. At the World Summit for Children (New York, 1990) and the International Conference on Nutrition (Rome, 1992) most of the members of the United Nations signed a declaration to eliminate vitamin A and iodine deficiencies and reduce rates of iron-deficiency anemia by one-third by the year 2000. Progress has been made in raising awareness and developing strategies [1, 3]. But except for the improvement made with regard to iodine, hidden hunger remains a persistent problem. It is important to recognize that single micronutrient deficiencies don't occur in isolation. Millions of people worldwide

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Mention of the names of firms and commercial products does not imply endorsement by the United Nations University.

suffer from deficiencies of multiple micronutrients at the same time. In addition, iron, vitamin A, and iodine have an overlapping impact on growth, development, performance, and health (table 1 [4, 5]).

We, in the private sector, have recognized that eradication of micronutrient malnutrition is an unmet consumer need. Thus, producing and marketing multiple-micronutrient-fortified (iron, iodine, and vitamin A) products will play an important role in improving people's health, self-esteem, and, ultimately, performance. However, there are several challenges in manufacturing and marketing products with meaningful levels of bioavailable and stable iron, iodine, and vitamin A without altering the accepted appearance and taste of the finally consumed product [6–8]. How do we successfully produce and market multiple-micronutrient-fortified products that will have a meaningful impact on the target population? How do we develop and implement an affordable and sustainable fortification program?

Micronutrient fortification of foods

During the last 15 years, The Procter & Gamble Co. (P&G) has been working on developing micronutrient fortification technology and products that meet the need of a large segment of the population in developing countries. During these years, we have learned that fortifying foods with micronutrients is more than adding fortificants, putting them in a package, and marketing them. Based on our experiences as well as learning from others, we have developed a model called "Sustainable Food Fortification Program," the success of which is dependent on the integration of multiple key elements (fig. 1). Thus, for food fortification to succeed, the model must include the following: (a) identification of deficiency among the target groups, (b) development of fortification technology/products to meet the need, (c) evaluation of the product's impact on alleviating the deficiencies, (d) manufacturing and distribution of the products, and (e) education of consumers about the benefits of fortified products and

the adverse effects of micronutrient malnutrition. All of these elements are potential barriers to the success of a micronutrient-fortification program. They should not be only identified but also addressed during the different stages of the fortification program. We have used the "Sustainable Food Fortification Program" in developing a multiple-micronutrient fortification technology called GrowthPlus®. The GrowthPlus/CreciPlus® technology has been used to formulate a powder fruit drink, which was marketed in Venezuela as NutriStar®, and earlier test marketed in the Philippines as NutriDelight.®

Establishing strategic alliance with the public sector

We recognized that in the private sector we don't have adequate capability to deliver a sustainable multiple-micronutrient fortification program by ourselves. Thus, it is critical that a strategic alliance is established among the major stakeholders [1, 7, 8]. As shown in figure 2, the major stakeholders include the scientific community, government, international agencies, non-government organizations (NGOs) and industry [8]. When it comes to improving the lives of children and women through the eradication of micronutrient malnutrition, these stakeholders have a common mission and goal, which is the elimination of micronutrient malnutrition. It is important to recognize that each stakeholder brings unique and complementary skills. Forging alliances between the public and the private sectors will not only benefit the parties involved, but more importantly will deliver a sustainable micronutrient-fortification program by leveraging each party's strength.

Our micronutrient fortification technology and the development of fortified powder fruit drink is, in fact,

TABLE 1. Consequences of iron, vitamin A, and iodine deficiencies

	Iron deficiency	Vitamin A deficiency	Iodine deficiency
Growth	↓	↓	↔
Mental ability	↓	↔	↓
Strength	↓	↔	↓
Mortality/morbidity	↑	↑	↔
Economic development	↓	↓	↓

Sources: Scrimshaw [4], Underwood [5].
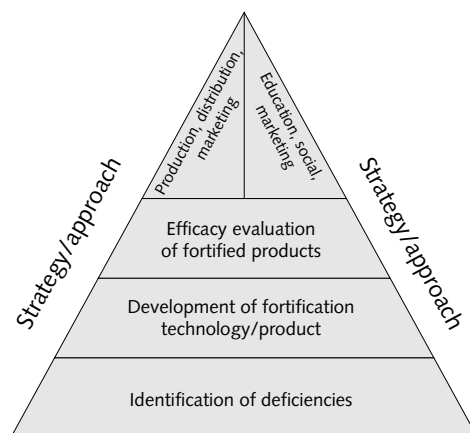Legend: ↓ decrease, ↑ increase, ↔ no change

FIG. 1. Sustainable micronutrient fortification program model

FIG 2. Micronutrient fortification strategy: Public-private partnership [8]

an outcome of public-private partnership that has been ongoing for the last 10 years (fig. 3). It began with Dr. Michael Latham's visit to P&G's Miami Valley Laboratories Technical Center in Cincinnati to give a seminar on micronutrient malnutrition. This initial partnership between Cornell University (Ithaca, New York) and P&G (Cincinnati, Ohio) further grew with the addition of the United Nations Children's Fund (UNICEF, New York), Micronutrient Initiative (MI, Ottawa, Canada), Tanzania Food & Nutrition Center (TFNC; Dar es Salaam, Tanzania), The University of Chile (Santiago, Chile), and the Nutrition Center of the Philippines (NCP, Manila, Philippines). The nutrient

composition in the fortified powder drink and the clinical studies conducted in Tanzania [9, 10] are all an outcome of this public-private partnership.

Micronutrient fortification technology development

It has been more than four decades since food fortification has been recommended as one of the preferred long-term approaches in eradicating nutrition deficiencies. However, its success, particularly in developing countries, has been very limited. One of the major challenges has been lack of affordable and easy-to-use fortification technology [6–8]. During fortification, we are bringing a vehicle (food or beverage) and the fortificants (vitamin or mineral sources) together. Because these are chemical moieties with functional groups, there is an interaction. It is this interaction that causes the development of undesirable taste (e.g., metallic aftertaste, rancidity), unacceptable appearance, poor stability, and significantly reduced bioavailability [6–15].

To find solutions, we have evaluated the chemical properties of different micronutrients (particularly iron, iodine, and vitamin A) that are used commonly in food fortification. With iron fortification the challenges include metallic aftertaste, off-color, off-flavor, vitamin/ flavor degradation, and poor bioavailability [6–8, 11–18]. These undesirable attributes are reflections of the chemical properties of iron. As a member of the transition elements, iron is known to undergo
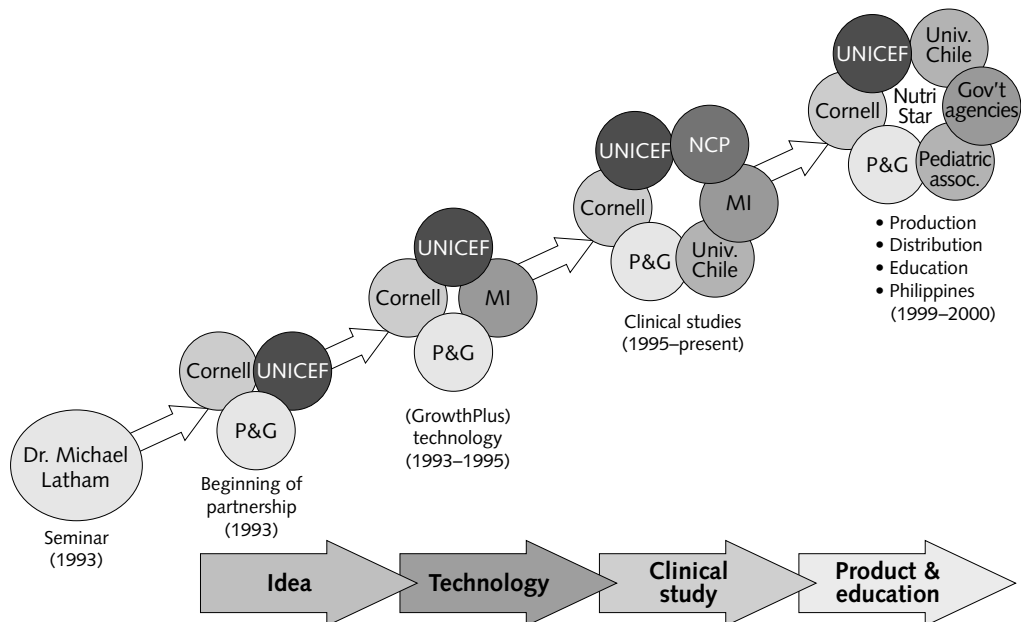

FIG. 3. Public-private partnership: "The fortified powder story"

an oxidation-reduction reaction. The challenge with delivering both vitamin A and iodine is linked mainly to stability. Both nutrients have poor stability during processing, storage, and cooking. Because of its multiple double bonds, vitamin A is sensitive to light and oxygen [12]. On the other hand, iodine undergoes oxidation-reduction; thus, it is easily lost (escapes as iodine gas) when exposed to excess moisture and temperature [13]. Further complicating the matter is that the degradation of vitamin A and iodine is accelerated by the presence of bioavailable iron as a fortificant [13].

The challenges in overcoming these multiple difficulties of delivering bioavailable/stable multiple micronutrients via a single vehicle were addressed by developing a fortification technology called "GrowthPlus.®" This unique technology delivers better-absorbed and utilized iron, vitamin A, and iodine (plus other vitamins and minerals) without compromising taste, color, and product and vitamin stability. This was accomplished by understanding and analyzing the factors that influence the reactivity, stability, and bioavailability of the micronutrients in a food/beverage-based delivery system. Based on the chemical properties of the three micronutrients (iron, vitamin A, and iodine), a delivery-system model called "Lock-Unlock" was developed. Thus, during the "lock" stage the nutrients remain stable (unreactive) during manufacturing/process, storage, and consumption of the fortified product by delivering them via chelation/reduction and/or encapsulation approaches. The stabilization of iron via the GrowthPlus® technology is shown in figure 4. Chelation was used to prevent the metallic aftertaste usually associated with mineral fortification. The iron-mediated off-color development, which is the result of either iron oxidation from ferrous to ferric or its interaction with the vehicle components (e.g., polyphenols), was prevented by creating an environment that keeps iron in the ferrous form. This is accomplished by optimizing both the pH and level of reducing agents by which the iron remains to stay in the ferrous form. During the

"unlock" stage, the iron delivered via the GrowthPlus® technology is released (becoming bioavailable) following the ingestion of the product. This has been demonstrated through repeated clinical studies (8–10, 15).

Technology evaluation

The effectiveness of the GrowthPlus® technology in keeping the iron sources (ferrous bis-glycinate and ferrous fumarate) stable has been tested by formulating various prototypes. They include water, chocolate milk, and baby cereal. Fortification with iron that contains multiple micronutrients was done with and without the GrowthPlus® technology. The results (not shown here because the color changes cannot depicted in black and white) demonstrated that in the absence of iron fortification, the water, chocolate milk, and baby cereal containing banana were clear, brown, and off-white, respectively; however, addition of iron (without using the GrowthPlus® technology) caused the water to be rusty, the chocolate milk to become brownish-gray, and the baby cereal to turn green. In contrast, when the fortification of those same prototypes with the same iron source was delivered via the GrowthPlus® technology, the development of off-color was completely prevented.

Product formulation

The success of any fortification program is dependent on identifying the right vehicle(s) and using a fortification technology that delivers the critical micronutrients without compromising bioavailability, stability, taste, and appearance of the finally consumed product [6–8]. Thus, the multiple micronutrients delivered via the GrowthPlus® technology must be formulated into products that are commonly consumed by target groups. Data obtained from market research surveys

• Poor solubility
• Off-color development
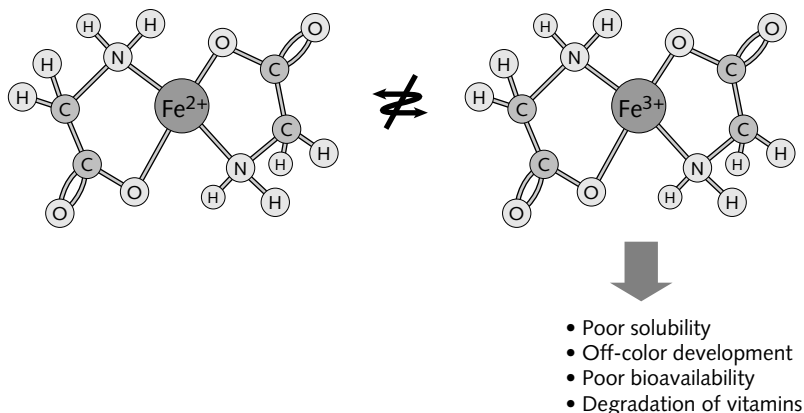• Poor bioavailability
• Degradation of vitamins

FIG. 4. Stabilization of iron by the GrowthPlus® Technology

showed that fruit-flavored drinks are not only well liked by the target groups but also commonly consumed globally (Compton DB, personal communication, 1998).

P&G developed the fortified powder fruit drink called NutriStar® by combining the GrowthPlus® fortification technology and a unique fruit juice flavor system (fig. 5). Thus, the fortified powder fruit drink consisted primarily of sweeteners, thickeners, clouds, acidulent, natural fruit flavors, and GrowthPlus® (iron containing multiple-micronutrients). It is important to recognize that the nutrition formula of the fortified powder fruit drink was developed to fill the nutrition gap in developing countries [19, 20]. The amount delivered (per single serving) through a fortified product is dependent on the regulatory laws of the country and the prevalence of the micronutrient deficiency. Hence, a single serving of the fortified powder fruit drink is usually formulated to deliver (in percentage of US recommended dietary allowance) 20–30% of iron, 15–35% of vitamin A, 25–30% of iodine, 25% of zinc, 100% of vitamin C, and 15–25% of B vitamins (folic acid, B_{12}, B_6, B_2, and niacin). During the last 6 years, the product attributes (taste, appearance, stability, and bioavailability) of the fortified powder fruit drink/NutriStar® have been evaluated prior to its introduction into the market place.

Product acceptance evaluation

For the fortified product to have an impact in combating micronutrient malnutrition, it first has to be consumed by the target groups. To be consumed, however, the addition of the fortificants (premix) should not change the appearance and taste of the product that is finally consumed [11]. Thus, the first evaluation work was on the sensory attributes of the finally consumed beverage, conducted via a 5-day home-use test among Filipino households. The overall acceptance of the fortified powder drink with the GrowthPlus® was compared with a placebo (product with the same appearance and taste but without multiple-micronutrient fortification). The subjects were asked questions about the overall product acceptance, flavor, and color during the 5-day use test. The findings showed the multiple-micronutrients (including iron, iodine, vitamin A) delivered via GrowthPlus® fortification technology had no significant effect on the flavor, color, and overall acceptance of the finally consumed fruit drink (table 2).

Nutrient stability evaluation

The fortified powder drink contains three minerals (iron, zinc, and iodine) and eight vitamins (vitamin A, vitamin E, vitamin C, niacin, B_6, B_2, folic acid, and B_{12}). How stable are these multiple micronutrients during the shelf life of the product? With iron and zinc, stability is not an issue; what is added will be there. However, with iodine and vitamins (such as vitamin A), poor

TABLE 2. Effect of GrowthPlus® on the acceptance of fortified powder fruit drink

Parameters	Fortified powder fruit drink	Nonfortified powder fruit drink
Overall rating[a]	44	45
Attribute rating[a]		
Orange flavor	43	46
Aftertaste	40	44
Color	44	48

a. Ratings used a five-point scale (excellent, very good, good, fair, poor). Average ratings are calculated using weights as follows: $(((N_{ex} \times 100) + (N_{vg} \times 75) + (N_{gd} \times 50) + (N_{fr} \times 25))/N_{total}) \times 100$

There is no significant difference between the fortified and the nonfortified powder beverage at $p < .05$
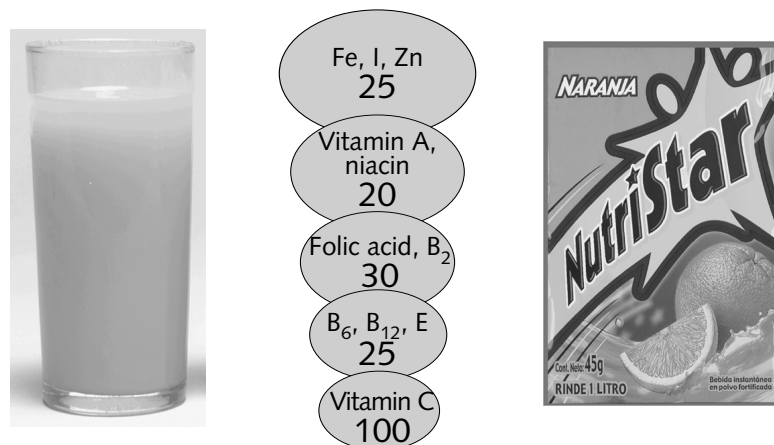

FIG. 5. Fortified powder fruit drink/NutriStar®: (Nutrient composition/serving in %Venezuelan RDA)

stability is a serious problem. The stability of the vitamins and minerals in the fortified powder fruit drink and the finally consumed reconstituted beverage was evaluated as a function of storage time.

The fortified powder fruit drink was packaged in a sachet and stored in temperature-controlled rooms for up to 1 year. As shown in table 3, all nutrients (added as GrowthPlus®) including vitamin C, iodine, folic acid, and B_{12} were stable after 1 year of storage at ambient temperature. The percent recovery ranged from 91.5% for vitamin A to 113.9% for vitamin B_6. It is important to note also all values after 1 year of storage are above the targeted value (claimed values in the product).

The fortified powder fruit drink is consumed after being reconstituted with added water. What is the stability of the nutrients in the reconstituted fortified powder fruit drink? The stability of the major micronutrients (namely, vitamin A, vitamin C, riboflavin, and iodine) that are known to be sensitive to degradation in aqueous delivery systems was further evaluated after the fortified powder fruit drink was reconstituted. The results obtained after 1-hr and 24-hr storage at ambient temperature are shown in table 4. As expected, there was no change in the iron level. Riboflavin, vitamin C, and vitamin A showed little or no degradation. However, the level of iodine in the reconstituted beverage was decreased by 21% and 16% after 1 hour and 24 hours, respectively. Taking the target value into consideration, the reconstituted fortified powder drink delivers the iodine level claimed on the package. Results in the literature have shown that vitamins and iodine are sensitive to degradation, particularly in aqueous delivery systems [12–14]. Furthermore, such degradation is further accelerated by the presence of divalent ions, particularly iron and copper. The stability observed in both the powder and beverage forms is due to the ability of the GrowthPlus® technology to keep the multiple micronutrients in a stable and/or non-reactive form.

Bioavailability evaluation

Most of the vitamins and iodine have adequate bioavailability as long as they are stable [21, 22]. However, for minerals such as iron, their bioavailability is dependent on the source vehicle and the diet consumed with it [6–8, 11, 16, 17]. Thus, once good-tasting multiple-micronutrient-fortified products are developed, it is critical that the bioavailability of the iron is evaluated. The bioavailability of the iron from the fortified powder fruit drink was determined by using a double isotope labeling technique [16]. The study was done in collaboration with Dr. Tomas Walter at the University of Chile. The treatments included the following: (a) fortified powder beverage alone and (b) fortified powder beverage with rice. As shown in figure 6, the absorption values were normalized to that of a standard ferrous ascorbate (40% absorption). Furthermore, comparison was made with the other common dietary iron sources [16–18]. When the reconstituted fortified powder fruit drink was consumed alone, 23.4% of the iron was absorbed. This is comparable to that absorbed from meat, and about five times that of milk fortified with ferrous sulfate [16–18]. However, when consumed with rice, the percent of iron absorbed was reduced by about half (23.4% vs 10.7%). Although there is a significant

Table 4. Nutrient stability from a reconstituted fortified powder fruit drink[a]

	Time 0	1 h	24 h
Vitamin A (IU)	499.5	494.5 (99%)	479.5 (96%)
Vitamin C (mg)	91.8	86.5 (94%)	76.9 (84%)
Iron (mg)	4.5	4.5 (100%)	4.6 (102%)
Riboflavin (mg)	0.3	0.32 (107%)	0.38 (127%)
Iodine (µg)	47.2	37.3 (79%)	39.8 (84%)

a. Analysis was done on fortified powder drink beverage prepared by dissolving 25 g powder fruit drink in 180 ml water.

Table 3. Nutrient stability in fortified powder fruit drink (in 100 g)[a]

Nutrients	Initial	12 months	% recovery after 12 months	% target value after 12 months
Iron (mg)	54.3	54.8	100.9	140.9
Vitamin A (IU)	10963	10030	91.5	139.3
Iodine (µg)	590	582	98.6	143.1
Vitamin C (mg)	899	988	110.0	148.2
Zinc (mg)	49.6	49.6	100.0	118.9
Folic acid (µg)	797	873	109.5	132.1
Vitamin B_{12} (µg)	8.6	8.8	102.3	157.1
Vitamin B_6 (mg)	6.5	7.4	113.9	132.1
Vitamin B_2 (mg)	6.2	5.9	95.2	115.7
Niacin (mg)	33.2	32.0	96.4	115.1
Vitamin E (mg)	31.3	31.9	101.9	102.9

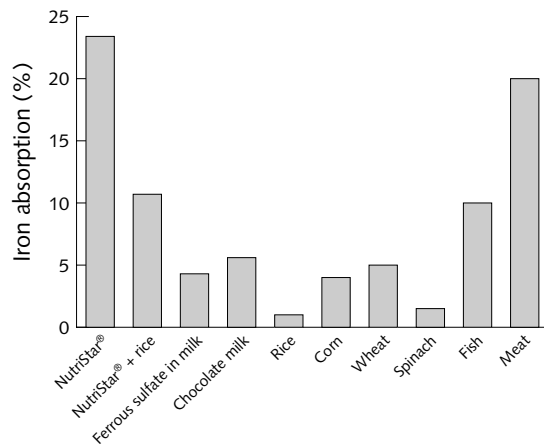a. The samples were stored in a temperature-controlled room at 70°F.

FIG. 6. Iron absorption from fortified powder fruit drink (NutriStar®) and other iron sources

reduction of iron absorption by rice, the bioavailability value is still comparable to that of iron from fish, which is accepted as a good source of bioavailable iron.

Product efficacy evaluation

Conducting an effectiveness trial among the target groups, particularly when it is done before the product is nationally distributed is important for the success and sustainability of a fortification program. It has practical implications, because it measures the impact after repeated consumption of the fortified product on improving nutrition status. The multiple-micronutrient-fortified powder fruit drink has been

evaluated by randomized, double-blind, placebo-controlled clinical studies in schoolchildren and pregnant and lactating women [8–10, 23, 24].

Production and distribution of fortified products

Currently, many of the multiple micronutrient fortification programs and research focus mainly on surveys, development of fortified product prototypes, and evaluation (stability, bioavailability, and efficacy). However, the impact of any fortified product in alleviating micronutrient malnutrition will occur only when the fortified product is produced, distributed in the marketplace, and consumed by the target groups. We believe this step is the least recognized bottleneck in the success of any fortification program. This final stage of the sustainable fortification program model includes production/scaling up, packaging, quality control, and distribution. Here, the private sector is the major player.

Our GrowthPlus® technology-based multiple-micronutrient-fortification program has already reached a milestone. The fortification technology developed, the clinical data generated, and the public-private partnership resources invested have been taken to a higher level, which includes scaling up, manufacturing, distribution, and marketing. The outcome, which is a fortified powder fruit drink named NutriStar,® has been in production and distribution for more than a year in Venezuela.

NutriStar® is manufactured by following a written procedure and good manufacturing practices (GMP). A quality assurance & control (QA&C) program, which

TABLE 5. Key elements in quality assurance program

> » *Finished product specification and description:* Quality has to be built into the fortified product. Thus, before the product is manufactured, both the specification and description of the finished product must be established. Subsequently, products are manufactured by following written procedures known as standard operating procedures (SOP). Based on the claim to be made, the type and level of the minerals and the form and source of fortificants are specified.
> » *Starting materials:* The quality of the starting materials for both the product and packaging play an important role in the quality of the final mineral-fortified product. The fortificants should meet established specifications. In addition, purchases are made from approved suppliers that follow good manufacturing practices (GMPs). Once received, the fortificants are recorded and stored as specified under appropriate conditions.
> » *Production and packaging:* The quality of manufacturing and packaging determines the quality of the final product. The product is made by following GMPs. The fortificants are added into the product formulation by using specified procedures and equipment. The amount of each fortificant added is recorded. Finally, the amount in the finished product is verified by using a validated analytical method.
> » *Release of finished product:* The product released for distribution should meet all finished product specifications. This includes the safety of the product and the level of the nutrients claimed. There should be a system for (a) monitoring and correcting deviations from specification and (b) identifying the product in case there is a complaint from the consumer.
> » *Documentation:* Accurate recording is essential for (a) identifying and correcting deviations, (b) recalling a product with serious problems, and (c) making an improvement on the quality of the product.
> » *Training:* All personnel involved in the development, manufacturing, packaging, and storing of the fortified product should be trained in quality assurance.

Source: Mehansho and Mannar [7].

includes the major key elements, has been already built into the production of the fortified powder drink (table 5). The objective of the QA&C program is to deliver a safe fortified product with nutrient levels as claimed on the package during the shelf life of the product. Note that the packaged NutriStar® is released for distribution only after meeting the finished product specification (i.e., safety and nutrient levels). The acceptance and consumption of NutriStar® by the Venezuelan population is meeting P&G's expectations. Consumption data for 12 months show that about 120 million servings of NutriStar® have been sold. This translates to a production and consumption of 1,080 metric tons of NutriStar® in 1 year.

Education and social marketing

Both education and raised awareness are key to the success of a sustainable micronutrient-fortification program. The objective of such a program is to provide simple, friendly, and effective messages to professionals (e.g., doctors, nutritionists, health workers), policymakers, and the target population on the prevalence and consequences of micronutrient malnutrition and the benefits of the micronutrient-fortified products. Public-private partnership is critical for the education program to be successful. This can only be accomplished by leveraging the expertise and resources of the stakeholders from both the private and public sectors. In the Philippines during the test market of NutriDelight, a strategic alliance between the public sector (UNICEF, Nutrition Center of the Philippines, National Nutrition Council, Ministry of Health and Ministry of Education) and P&G was established. The outcomes of this particular alliance include micronutrient education via television, a micronutrient

symposium, and an interactive/integrated educational program called BIDA. Currently, the micronutrient educational program (BIDA) is widely distributed and utilized in the Philippines (Florentino Solon, personal communication, 2002).

Conclusion

Eradication of micronutrient malnutrition, even though it seems formidable, can be accomplished. Based on our and others' experience, an effective and sustainable micronutrient-fortification program will require a holistic and integrated program. The program should address the multiple barriers identified in the "Sustainable Food Fortification Model" and leverage the untapped expertise and strength of the public-private partnership based on a win-win situation. The development of GrowthPlus® fortification technology and the fortified powder fruit drink known as NutriStar® in Venezuela has been accomplished by following the "Sustainable Food Fortification Model" and utilizing the resources and expertise of the public-private partnership. The highlights include the following: (a) fortification with meaningful levels of the most deficient micronutrients without altering the taste of the finally consumed beverage by using the GrowthPlus® technology; (b) proving that repeated consumption of the product improves the micronutrient status of the target population; (c) manufacturing by following GMP and QA&C program, and (d) distributing and marketing the product. Finally, after several years of fruitful, collaborative work, we believe that we have reached the stage where this innovative approach to controlling prevalent micronutrient deficiencies can be successfully used in the marketplace.

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Efficacy trials of a micronutrient dietary supplement in schoolchildren and pregnant women in Tanzania

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Abstract

Traditionally, the main strategies used to control micronutrient deficiencies have been food diversification, consumption of medicinal supplements, and food fortification. In Tanzania, we conducted efficacy trials using a dietary supplement as a fourth approach. These were randomized, double-blind, placebo-controlled efficacy trials conducted separately first in children and later in pregnant women. The dietary supplement was a powder used to prepare an orange-flavored beverage. In the school trial, children consumed 25 g per school day attended. In the pregnancy trial, women consumed the contents of two 25-g sachets per day with meals. This dietary supplement, unlike most medicinal supplements, provided 11 micronutrients, including iron and vitamin A, in physiologic amounts. In both trials we compared changes in subjects consuming either the fortified or the nonfortified supplement. Measures of iron and vitamin A status were similar in the groups at the baseline examination, but significantly different at follow-up, always in favor of the fortified groups. Children receiving the fortified supplement had significantly improved anthropometric measures when compared with controls. At four weeks postpartum, the breast milk of a supplemented group of women had significantly higher mean retinol content than did the milk of mothers consuming the nonfortified supplement. The advantages of using a fortified dietary supplement, compared with other approaches, include its ability to control several micronutrient deficiencies simultaneously; the use of physiologic amounts of nutrients, rather than megadoses that require medical supervision; and the likelihood of better compliance than with the use of pills because subjects liked the beverage used in these trials.

Key words: Iron, micronutrients, powder beverage, pregnancy, supplement, Tanzania, vitamin A

Introduction

Micronutrient deficiencies, particularly of iron, iodine, and vitamin A, have been recognized for many years as serious health problems in developing countries [1], including in Tanzania [2]. Well over two billion people worldwide are believed to suffer from these deficiencies, with women of reproductive age and young children at greatest risk. It is also known that in many developing countries, zinc deficiencies are also prevalent; inadequate intakes of vitamin C may adversely influence iron absorption; vitamin E is an important antioxidant; and the following vitamin B-complex deficiencies also have adverse results: riboflavin (widespread ariboflavinosis), vitamin B_{12} (anemia), vitamin B_6 (neuropathies), folate (anemia and spina bifida), and niacin (pellagra). Very few developing countries have in place strategies to control these micronutrient deficiencies.

Standard strategies to overcome micronutrient deficiencies

Despite the wide prevalence and devastating consequences [3] of micronutrient deficiencies worldwide, the established approaches to control them have remained much the same for more than three decades and consist mainly of the following three strategies:

» *Dietary diversification.* Clearly the aim of nutritionists is to ensure that people consume a variety of foods that together provide adequate quantities of all the essential micronutrients necessary for health. Actions

taken may include nutrition-education programs to achieve behavioral change, as well as increasing and diversifying regional and/or household production and consumption of micronutrient-rich foods.

» *Food fortification.* The addition of a micronutrient to a food item that is widely consumed by a population at risk of a deficiency has been a widely used strategy for many years in industrialized countries. The classic example is the iodization of salt now practiced in many countries. Other examples are vitamin A added to dairy products and iron to baby cereals.

» *Medicinal supplementation.* This includes the provision of a micronutrient often through the health-care system usually in the form of a pill, liquid, or injection. It may include (a) periodic administration of megadoses of a specific micronutrient, such as vitamin A or iodine, or (b) regular provision of medicinal amounts of a micronutrient in amounts much higher than the recommended daily intakes (RDI), for example, iron supplements during pregnancy.

Disadvantages and limitations of standard strategies

These three strategies have had both successes and failures, and each has disadvantages and limitations. Many agree that food diversification offers the best long-term approach that is likely to be sustainable [4]. But often it requires either major change in agricultural production, including home gardens, or in higher incomes for the poor, allied with nutrition education. Therefore, progress is slow in many non-industrialized countries, and in some African countries with a deteriorating economic situation, food diversification is unlikely to reduce substantially micronutrient deficiencies in the near future. The conditions needed for successful fortification vary depending on the foods widely eaten in a country and the nutrients being considered for fortification. In some countries several commonly eaten foods do pass through commercial processing where fortification is feasible. Salt iodization has greatly reduced iodine deficiency disorders in many countries, including Tanzania. But in many non-industrialized countries it is difficult to find a suitable food vehicle to fortify with iron or vitamin A. To be suitable for fortification, a food must be consumed regularly by those at risk of the deficiency—often children and women in poor families. Especially in rural areas, those suffering from micronutrient deficiencies may purchase few manufactured or processed foods.

There are two kinds of medicinal supplements. First there are those taken in pharmacologic doses daily or at frequent intervals, and second are those prescribed to be consumed in megadoses at intervals of 4 to 24 months. Ferrous sulfate and folate are examples of the former, and vitamin A and Lipiodol® (iodinated poppy seed oil) and oral iodine are examples of the latter. Medicinal supplementation is dependent on a delivery system, which is often relatively costly if the supplement is to reach those at risk. Other problems include poor compliance, which is common with iron prescribed during pregnancy, and low participation rates, such as when massive dose vitamin A supplements are offered over time.

Common problems in implementing the standard strategies

A World Bank review of micronutrient programs [5] found three common problems arising from the implementation of any or all of these strategies: (1) lack of appropriate consumer demand; (2) lack of appropriate delivery infrastructure with adequate access for poor women and isolated populations; and (3) lack of honest, efficient, and technically competent enforcement systems for food fortification.

Appeal of micronutrient dietary supplements as a fourth approach

Micronutrient dietary supplements offer a fourth approach and one that can control several micronutrient deficiencies simultaneously. This approach differs from medicinal supplementation in that several micronutrients are provided at the same time; the micronutrients are provided in physiologic amounts, rather than in megadoses; the supplements can be self "prescribed" or purchased in the marketplace, rather than through the healthcare system; and they are usually pleasant to take, and therefore avoid problems of compliance often associated with medicinal supplements. However, micronutrient dietary supplements have not been very widely used to control common deficiencies in developing countries. The dietary supplement we used has some features of fortification and others related to more common forms of supplementation.

Trials of a micronutrient dietary supplement in Tanzania

In the Dodoma Region of Tanzania, two separate double-blind, placebo-controlled field efficacy trials have been completed using a multiple-micronutrient-fortified dietary supplement. The first trial [6, 7] was conducted with young primary schoolchildren and the second with pregnant women, some of whom were followed postpartum during 4 weeks of lactation [8].

Micronutrient deficiencies including iron deficiency, vitamin A deficiency, and iodine deficiency disorders are recognized as important public health problems in Tanzania [2]. The trials were collaborative involving

the Tanzania Food and Nutrition Centre (TFNC), Cornell University (Ithaca, NY, USA), United Nations Children's Fund (UNICEF), the Micronutrient Initiative (MI) (Canada), and The Procter & Gamble Co. (P&G) (Cincinnati, Ohio, USA).

The dietary supplement used was a fortified powdered fruit drink. It was developed and produced by scientists at P&G in Ohio, especially for these trials in Tanzania. However nutritionists at TFNC and Cornell University, in consultation with P&G and others, made the decision about which micronutrients to include and in what quantities.

The dietary supplement was supplied to the research team in individual-serving paper sachets each containing 25 g of a fine white powder. The contents of a sachet, when added to 250 ml of water, turned orange and produced a pleasant tasting orange-flavored beverage. The micronutrient content of each fortified sachet is shown in table 1. As indicated in the table, niacin was not included in the supplement for the school study, but was included for the pregnancy trial.

For each trial, P&G provided an equal quantity of nonfortified supplement (placebo) identical in appearance and taste to the fortified supplement. The sachets containing the fortified and nonfortified beverage supplements differed only in the color of the package. The study participants as well as the research team did not know which sachets were fortified and which were not until the results had been analyzed, when the code was broken. Different-colored sachets were used for each of the trials.

Table 1. Nutrient levels in each micronutrient fortified sachet[a]

Nutrient	Amount of nutrient in 25 g sachet	% RDI[b] Value per sachet
Iron (Ferrochel®)	5.4 mg	30
Vitamin A (retinyl palmitate)	1,750 IU	35
Iodine	45 µg	30
Zinc	5.25 mg	35
Ascorbic acid	72 mg	120
Riboflavin	0.6 mg	35
Folic acid	0.14 mg	35
Vitamin B$_{12}$	3 µg	50
Vitamin B$_6$	0.7 mg	35
Vitamin E	10.5 mg	35
Niacin[c]	5.0 mg	30

a. In the school trial, children consumed one sachet per school day attended. Women in the pregnancy trial were instructed to consume two sachets per day, one with the morning and a second with the evening meal.
b. RDI = recommended daily intake
c. Niacin was not included in the school trial.

Efficacy trial in schoolchildren

This was a randomized, double-blind, placebo-controlled efficacy trial. The children who participated were recruited from six rural primary schools in Mpwapwa District in the Dodoma Region of Tanzania. The main objective of the trial was to determine whether a dietary supplement providing 10 micronutrients in physiologic amounts resulted 6 months later in differences in measures of iron status, serum retinol, and child growth when compared with children receiving a nonfortified supplement identical in appearance and taste. Children were randomly assigned to be in either the fortified or nonfortified group. The children, teachers, and researchers did not know which sachets—the blue ones labeled "J" or the green ones labeled "K"—were fortified. The content of each sachet was added to 250 ml of previously boiled water to form a pleasant tasting orange-flavored beverage. During the morning break children lined up according to the two groups and were served their beverage. Teachers recorded attendance in the compliance notebooks.

The results presented here relate mainly to the 774 young primary schoolchildren examined at baseline and 6 months later at the follow-up examinations. All had participated and consumed on each school day attended one sachet of either the fortified or nonfortified beverage. Details relating to subject selection, methodology used, and detailed results in relation to iron nutrition status, serum retinol levels, and anthropometry have been reported elsewhere [6]. Baseline characteristics of children in the fortified and nonfortified groups were similar in terms of mean age, gender distribution, anthropometric measures (weight, height, and body mass index [BMI]), hemoglobin and serum retinol levels, and presence of helminthic infections in their stool samples.

Baseline measurements of both groups

The beverage was very well liked and consumption rates were very high. The percentage of days of possible consumption during the trial did not differ between the two groups (79.9% in the fortified and 81.1% in the nonfortified group). At baseline, 18.5% of the fortified group and 19.1% of the nonfortified group had hemoglobin levels below 110g/L. Findings show that 21.4% of the fortified group and 20.6% of the nonfortified group had serum retinol levels below 200 µg/L. Anthropometry showed that 50.5% of children in the fortified group and 49.5% of children in the unfortified group had height-for-age Z-scores below −2. In none of these measurements are the differences significant between the two groups at baseline.

Changes in hemoglobin, serum ferritin, and serum retinol levels

After 6 months, hemoglobin levels had declined

significantly in both the fortified and nonfortified groups, although the decline of 6.7 g/L in the nonfortified group was significantly larger than the decline of 3.2 g/L in the fortified group (table 2). We have discussed elsewhere [6] our belief concerning the reasons why hemoglobin levels declined in both groups between baseline and follow-up. We believe this was mainly a seasonal effect because the follow-up exams were performed at a time of year when food is often in short supply prior to the next harvest and a period when malaria transmission is very high. As shown, serum ferritin levels increased significantly in the fortified group, but there was no significant change in the nonfortified group. In those children with anemia at the baseline (Hb < 110 g/L [9]) there was a significantly higher rise in hemoglobin concentration (9.2 g/L) in the fortified group compared with a nonsignificant rise in the nonfortified group (0.3 g/L). At baseline, there was no significant difference in the percentage of children with anemia (18.5% versus 19.1%). At follow-up, there was a significant difference (chi-square = 0.005) in the percentage of children in the two groups who were still anemic (26.3% versus 35.6%). In terms of serum retinol determinations, the percentage of children in the fortified group whose serum retinol was below 200 µg/L declined from 21.4% to 11.3% between baseline and follow-up (table 3). This was a very significant improvement. In contrast, the percentage decline in those with deficient serum retinol levels was not significant in the nonfortified group.

Anthropometric-measurement changes

In terms of anthropometry, there were no significant differences in mean weight, height, and BMI between groups at the baseline examination [7]. However, at follow-up, incremental changes in weight (1.79 versus 1.24 kg, a difference of 0.55 kg); in height (3.2 cm versus 2.6 cm, a difference of 0.6 cm); and in BMI units (0.88 versus 0.53, a difference of 0.35) were significantly higher in the fortified compared with the nonfortified group (results not shown).

Efficacy trial in pregnant women

The pregnancy trial in the Dodoma Region in Tanzania in 1999 enrolled pregnant women attending six different clinics, five in Mpwapwa and one in Kongwa Districts [8]. At baseline, 579 women were screened; 140 were excluded mainly because their pregnancies were too advanced (50%) or because their hemoglobin levels were below 80 g/L (26%). Of the 439 women who enrolled in the study, the main results presented here relate to 259 women who both participated in the supplementation trial and who had not delivered 8 weeks after their initial examination. (Fifty-nine supplemented mothers delivered their infants before 8 weeks of follow-up had elapsed and another 121 women were lost to follow-up.)

The objective of the trial was to evaluate the effect of the micronutrient supplement on iron status, hemoglobin, and serum retinol levels. In a subgroup of women, breast milk was obtained 4 weeks postpartum to determine retinol levels.

At each clinic site, after the baseline examination, pregnant women were randomly assigned to receive either the micronutrient-fortified or the nonfortified dietary supplement. Each woman was carefully instructed on how to mix the contents of one sachet with about 250 ml of clean boiled water to produce a single serving of the orange-flavored beverage. They

TABLE 2. Concentrations of hemoglobin and serum ferritin in children at baseline and after 6 months of supplementation, and the respective changes compared with baseline

		Nonfortified			Fortified		
Endpoint	n	Mean (SD)	Paired t test p value	n	Mean (SD)	Paired t test p value	Between group p value
Hemoglobin (g/L)							
Baseline	376	119.7 (13)		373	119.2 (14)		.639
Follow-up	376	112.9 (15)		373	116.0 (13)		.001
Difference[a]		−6.7 (13)	.001		−3.2 (13)	.001	.001
Serum ferritin[b] (µg/L)							
Baseline	148	33.88 (30.97–37.83)		149	29.51 (29.97–33.02)		.054
Follow-up	148	36.31 (33.43–40.13)		149	45.71 (42.20–50.15)		.001
Difference		2.05 (28)	.180		15.90 (33)	.001	.001

a. Difference is mean within-individual incremental change between baseline measurements and measurements after 6-month intervention.
b. Geometric mean ± 95% confidence interval (CI).

TABLE 3. Percentage of children with serum retinol concentration below 200 μg/L in the fortified and nonfortified group at baseline and follow-up examinations

Serum Retinol % below 200 μg/L	n	Fortified %	n	Nonfortified %	Between group significance
Baseline	364	21.4	370	20.6	NS
Follow-up	364	11.3	370	19.7	.001
Difference		10.4		0.9	.001
Significance of difference		.001		NS	

NS = Not significant

were requested to consume two sachets daily, one with the morning and the second with the evening meal. Each woman was provided with a plastic mug and a 2-week supply of supplement and was requested to collect new supplies every 2 weeks at the clinic for the duration of the 8-week intervention period. During each follow-up visit they brought back the empty sachets that were counted, thus serving as one method of measuring compliance [10].

Baseline measurements of both groups

Data collected at baseline included assessment of gestational age; information on parity and gravidity of the current pregnancy; history of medical problems and health status; phlebotomy to collect 5 ml of blood (2 ml of serum) for immediate determination of hemoglobin and later analyses of serum ferritin and C-reactive protein (CRP) levels; finger-prick capillary blood to prepare dried spots on filter paper for subsequent determination of retinol and thyroid stimulating hormone levels; and anthropometric data, including height, weight, mid-upper arm circumference, and triceps skinfold thickness. Most of the appropriate measurements were repeated at the 8-week follow-up examination.

Similarities between groups

There was no significant difference at the baseline in terms of hemoglobin and serum ferritin levels of those women who completed the study when compared with those who did not. An equal number of subjects were lost from each treatment group. There were also no significant differences in the age, educational level, parity, gravidity, or anthropometric measurements in women in the two groups. Women in the group receiving the fortified supplement had a marginally higher gestational age when compared with those receiving the nonfortified supplement. The prevalence of parasitic infestation was low and did not differ between treatment groups, nor did history of malarial infection or additional iron supplementation. No significant differences were found in levels of thyroid stimulating hormone (TSH) between groups, or between baseline and follow-up examinations. Most subjects were using iodized salt.

Hemoglobin-level changes

At baseline, 61.4% of the study participants were anemic (hemoglobin level below 110 g/L [9]) with no significant difference between the experimental and the control groups. At the end of 8 weeks of supplementation, both groups experienced a decrease in the incidence of anemia. The proportion of anemic women in the control group declined from 59.1% to 48.5%. In contrast, women in the fortified beverage group experienced an almost 27% decline from 63.8% to 37%, producing a highly significant difference (P = .019) in the proportion of anemic women between the nonfortified and fortified groups at the end of the treatment period (48.5% versus 37%, respectively) (fig. 1).

Table 4 shows that both groups experienced a significant increase in hemoglobin concentration. However, mothers in the fortified-beverage group had a mean increase of 9 g/L while mothers in the nonfortified group had mean increase of only 4 g/L. Therefore, fortified group women experienced a 5 g/L significantly higher increase in hemoglobin concentration when compared with nonfortified group women (P = .015).
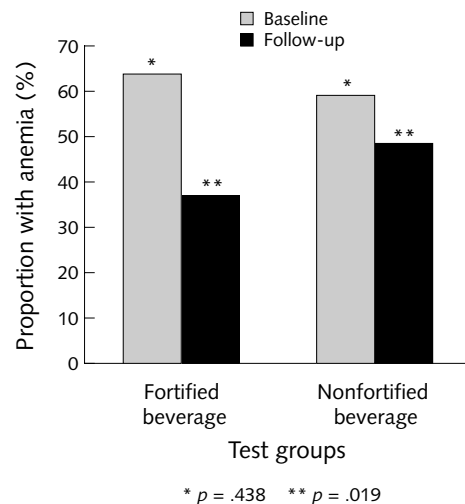

* p = .438   ** p = .019

FIG. 1. Comparison of proportion of women with anemia (hemoglobin < 110 g/L [9]) at baseline and at follow-up in the fortified and nonfortified beverage groups

TABLE 4. Hemoglobin, ferritin, and serum retinol concentrations in women before and after supplementation

Indicator	Fortified beverage				Nonfortified beverage (placebo)			
	n	Mean	(SD)	Sig.	n	Mean	(SD)	Sig.
Hemoglobin (g/L)								
Baseline	127	105	(14.2)		132	105	(14.9)	
Follow-up	127	114	(14.0)		132	109	(15.1)	
Difference	127	9		.000	132	4		.000
Ferritin (µg/L)								
Baseline	118	184.7	(2.31)		116	189.1	(2.4)	
Follow-up	118	215.1	(2.1)		116	169.2	(1.97)	
Difference	118	30.4		.012	116	−19.9		.166
Serum Retinol (µmol/L) (not delivered)[a]								
Baseline	116	1.04	(0.36)		126	1.00	(0.33)	
Follow-up	116	0.78	(0.27)		126	0.78	(0.29)	
Difference	116	−0.26		.000	126	−0.22		.000
Serum Retinol (µmol/L) (delivered)[b]								
Baseline	28	0.93	(0.29)		18	1.02	(0.34)	
Follow-up	28	1.08	(0.32)		18	0.96	(0.25)	
Difference	28	0.15		.078	18	−0.06		.509

a. Mother has not yet delivered at 8-week follow-up
b. Mother had delivered before 8-week follow-up

Changes in serum ferritin levels

As shown in table 4, there was no significant difference at the baseline in the mean ferritin concentration of the two groups (184.7 versus 189.1 µg/L). At the 8-week follow-up, however, the mean serum ferritin level was significantly higher (45.9 µg/L) in the fortified-beverage group than in the nonfortified group (P = .009). Mothers in the fortified-beverage group had a significant mean increase of 30.4 µg/L, while mothers consuming the nonfortified beverage experienced a nonsignificant mean drop of 19.9 µg/L. Therefore, the fortified beverage appeared to result in a net improvement in ferritin concentration.

Changes in serum retinol levels

The results of the serum retinol determinations, including the changes between baseline and follow-up examinations in both groups of subjects are also shown in table 4. Data are included for any woman in either group who had not delivered her infant, and also for the smaller number of women who had delivered prior to the completion of 8 weeks of supplementation. As shown in table 4 there was a decline in serum retinol levels between the baseline and follow-up examination prior to delivery in both groups. It is known that serum retinol levels decline during the last weeks of pregnancy and that it takes rather large doses of medicinal vitamin A to reverse this decline [11]. However, in those mothers who had delivered their infants, the mothers consuming the fortified supplement had a significant improvement in serum retinol levels (fig.

2), whereas there was a marginally significant decline in mean serum retinol levels in mothers receiving the nonfortified supplement. At follow-up, mothers who had delivered and were in the fortified group had mean serum retinol levels 0.12 µmol/L higher than similar mothers consuming the nonfortified supplement. In a separate analysis, we found that serum retinol levels were positively correlated with increases in hemoglobin [8], illustrating the importance of an adequate vitamin A status in the control of anemia.
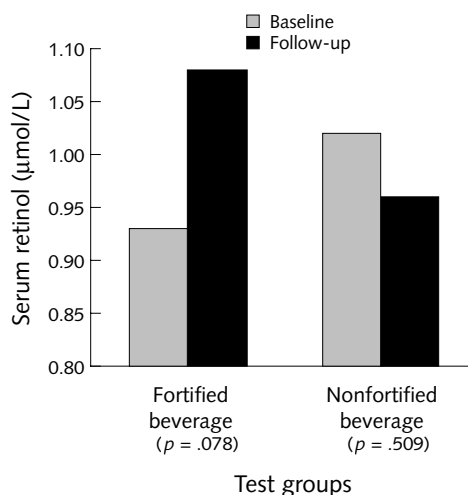

FIG. 2. Changes in serum retinol in women who had already delivered at the time of follow-up (N = 46)

Breast milk retinol levels

Samples of breast milk were obtained approximately 4 weeks postpartum in 50 mothers in the fortified group and 34 in the nonfortified group. The results are provided in table 5, which shows that mothers in the fortified group had mean breast milk retinol levels of 1.24 μmol/L compared with 1.06 μmol/L in mothers consuming the nonfortified beverage. The difference is highly significant. In a separate analysis, we found that serum and breast milk retinol levels were significantly positively correlated. Breast milk retinol levels were not significantly associated with other measures of nutrition status, such as hemoglobin or serum ferritin levels. Therefore, the results show that the fortified supplement was significantly associated with higher breast milk retinol levels.

Benefits of the micronutrient dietary supplement

These trials were initially designed to test the efficacy of a newly developed multiple-micronutrient supplement both in schoolchildren and in pregnant women. The results summarized above illustrate that the fortified supplement when compared with the nonfortified supplement had a positive impact on measures of iron (in terms of hemoglobin and serum ferritin levels) and vitamin A status (in serum retinol levels) in both children and women; it appeared to improve the growth of children; and it also seemed to increase levels of retinol in breast milk from mothers consuming the fortified beverage.

As previously mentioned, the major micronutrient deficiencies identified in Tanzania are iron, iodine, and vitamin A deficiency [2]. The ultimate objective of the trial was not only to deliver adequate levels of bioavailable iron, stable vitamin A, and iodine via the beverage that schoolchildren and pregnant women found to be highly palatable and pleasant to take, but also to provide in physiologic amounts many other essential minerals and vitamins, including zinc, vitamin C, and folate (table 1). From unpublished dietary evidence, daily consumption of the beverage raised the intakes of the 10 micronutrients (11 in the pregnancy trial) to levels above accepted recommended dietary intakes. Therefore, the multiple-micronutrient-fortified powdered fruit drink delivers nutrients in a tasty beverage that is convenient and affordable.

TABLE 5. Comparison of breast milk retinol (μmol/L) in mothers belonging to the two treatment groups

	Fortified		Nonfortified	
	N	Mean (SD)	N	Mean (SD)
Breast milk retinol[a]	50	1.24 (.34)	34	1.06 (.30)

a. t = 2.574, df 82, p = .012

Product acceptance

During the pregnancy trial, we employed, with UNICEF support, a social anthropologist with extensive Tanzanian experience to examine social attitudes toward the use of this beverage supplement. We recognized that frequently a new health or nutrition intervention, even if scientifically demonstrated to be efficacious, does not assure that people are likely to accept or adopt the product tested. The anthropologist concluded [10], without qualification, that women (1) like the beverage as a delivery vehicle; (2) prefer this dietary supplement to pills such as ferrous sulphate, (3) consider it beneficial to health, and (4) are willing, and able, to utilize the supplement properly and follow instructions concerning its use.

We found that the Ministry of Health very frequently fails to make available iron and folate tablets to pregnant women, and in Tanzania (as is the case in many countries), it has been shown that compliance in taking these tablets is low. So our trial leads us to believe that a dietary supplement such as this would be popular, be widely consumed, and could have major benefits. In the case of Tanzania we are exploring ways to have it locally manufactured.

Micronutrient dietary supplements offer a viable fourth approach, one that can control several deficiencies using a single intervention. This approach is different from the three standard approaches mentioned earlier, because it delivers micronutrients that fill the nutrition gap via a vehicle that is, or becomes, well accepted by the target group.

Early successes in dietary supplementation

The supplementation of diets with a specific food substance high in one or more micronutrients recognized as potentially deficient in the regular diet is not a new concept. Up to about 60 years ago, children in industrialized or industrializing countries received a regular dose of cod liver oil to stave off the effects of vitamin A and D deficiencies. In the early 1900s, rickets (the consequence of prolonged deficient vitamin D intake or lack of sunshine) was very common among children in the poor communities of industrialized cities where the diets were comprised of a small range of foods and there was limited access to outdoor areas and thus direct sunlight. In some countries, on the shelves of remote, small rural and urban shops, one can still find bottles of a concoction of halibut oil high in vitamins A and D or of Ribena® (GlaxoSmithKline Group), to provide vitamin C. Glucosade, a supplement claiming to provide instant energy, is widely sold; its main nutrient is glucose. Other products, some labeled as "tonics," are widely available in many countries worldwide. However these supplements and tonics often do

not include those minerals and vitamins most lacking in local diets. Often, these products are a very costly way of providing micronutrients to target groups that have limited income.

In Europe and North America, the promotion of cod liver oil and other healthful dietary supplements empowered mothers with affordable options to prevent rickets in their children, and where such solutions were not affordable, those dietary supplements were available free of charge through public health clinics. The development of better health care systems, affordable and diversified food supplies, and a growing appreciation of the health benefits of outdoor play presumably also underlie the decline of rickets in industrialized countries [12]. Unfortunately, the concept of regular dietary-supplement consumption has not been translated from industrialized countries to the populations of nonindustrialized countries that continue to be at risk of, or suffer from, micronutrient deficiencies.

Recently in South Africa, a trial of a micronutrient-fortified biscuit was successfully tested and yielded positive results [13]. There is also extensive literature on the successful use of dietary or food supplements such as Incaparina in Guatemala to provide additional energy, protein, and other nutrients to children [14].

Implementing a new dietary supplement

In conclusion, the dietary-supplement strategy recognizes the key principles incorporated in one or all of the other three commonly used intervention methods as follows: behavioral change via social marketing, diversification of food intake, supply of specific vitamins in specific foods, and regular doses of vitamins and minerals specific to regionally or locally recognized deficiencies. These are the underlying mechanisms by which micronutrient deficiencies are addressed. Just as food diversification seeks to create a supply, demand, and taste for a new food item, so should the promotion of a dietary supplement; and, just as medicinal supplements aim to provide a significant (albeit pharmacologic) dose of specific nutrients, a well-developed supplement could do the same using physiologic amounts.

Dietary supplements may potentially overcome some of the problems identified with other approaches to micronutrient deficiencies. Where sufficient appreciation and desire for the food item is generated—developed through commercial marketing strategies—supply should be ensured through market demand. Political will and external, public resources are not necessary inputs, although they could be of benefit in generating a rapid development of demand and supply or for ensuring access through subsidies and/or free supply where income is not sufficient. The argument for a contribution from commercial manufacturers to the cost of subsidies and for social-marketing promotions should not be overlooked given the potential for longer-term sales development.

As with the dietary supplement practices of old, this approach can empower mothers and families with a healthful, care-giving practice that they control and can ideally access with security at reasonable cost. Importantly, it is technically possible to include several micronutrients within a single food item, thus the process of addressing a situation where there are several deficiencies is simplified—a clear advantage over current fortification and medicinal-supplementation strategies.

Other versions of the test product

The dietary supplement described here was produced by food scientists at The Procter & Gamble Co. in Cincinnati and was especially manufactured to contain the range and amount of micronutrients we requested for the trials in Tanzania. The same dietary supplement, also in the form of a powder to make a fruit-flavored beverage, has more recently been tested elsewhere, sometimes with alternative packaging and different flavoring other than orange. It has been extensively tested in the Philippines [15], is being manufactured and commercially marketed under the brand name NutriStar® in Venezuela (P&G), and is being tested in an efficacy trial in adolescent girls in Bangladesh.

Public-private partnerships

The Tanzanian trials described here provide an excellent example of public-private partnerships and true collaborative efforts. In the work in Tanzania, collaboration involved the TFNC; UNICEF staff based in New York, Nairobi, and Dar es Salaam; the Micronutrient Initiative in Canada; The Procter & Gamble Co.; Cornell University's Division of Nutritional Sciences; and importantly also local institutions and civil society in the Dodoma Region of Tanzania. This collaboration and long-term partnerships have been rewarding to all and have been maintained over many years.

Plan for overcoming micronutrient deficiencies in Tanzania

Tanzania is currently taking steps to address the serious problems of iron, vitamin A, and iodine deficiencies. Wisely, a variety of strategies are being used. Among the interventions being tried are iron and folate supplements administered to pregnant women; programs to deworm children in part to reduce anemia; fermentation and germination of grains to improve iron utilization and to reduce the action of phytates;

vitamin A supplementation in high-risk children in many health units; efforts to increase the production and consumption of carotene-rich foods; legislation to ensure iodization of salt from the major manufacturers; and other actions to address diseases, such as malaria, that influence nutrition status [16].

These two studies in Tanzania are considered an important first step in testing and further developing the mechanism of dietary supplementation for addressing micronutrient deficiencies. A distinction is being made here between medicinal supplements such as ferrous sulphate tablets and dietary supplements. Differences include the fact that medicinal supplements are taken under medical supervision and control, whereas dietary supplements for children are controlled by the mother or family, and for the pregnant woman by the mother herself. Another important difference is that this dietary supplement provided physiologic "doses" of 11 micronutrients, where medicinal supplements provide doses of micronutrients much above the RDI and often only one or two micronutrients per dose.

It is not expected or intended that this approach will replace current programs and strategies, but instead that it will provide policy makers, health planners, and, more importantly, mothers and families, with an additional option. The decision on which strategy to pursue or promote and how public dollars will be directed must be assessed on a case-by-case basis. Moreover, consistent with current understandings and experiences, which show that no single approach will be effective in all settings and at all times, the further development of this fourth option can provide an effective means to fill the gaps left by the other three approaches.

Acknowledgments

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Effect of a multiple-micronutrient-fortified fruit powder beverage on the nutrition status, physical fitness, and cognitive performance of schoolchildren in the Philippines

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Abstract

This study aimed to determine the effect of a multiple-micronutrient-fortified beverage on the micronutrient status, physical fitness, and cognitive performance of schoolchildren. The study was a randomized, double-blind, placebo-controlled trial of schoolchildren assigned to receive either the fortified or nonfortified beverage with or without anthelmintic therapy. Data on hemoglobin level, urinary iodine excretion (UIE) level, physical fitness, and cognitive performance were collected at baseline and at 16 weeks post-intervention. The fortified beverage significantly improved iron status among the subjects that had hemoglobin levels < 11 g/dl at baseline. The proportion of children who remained moderately to severely anemic was significantly lower among those given the fortified beverage. In the groups that received the fortified product, the median UIE level increased, whereas among those who received the placebo beverage, the median UIE level was reduced significantly. Iron- and/or iodine-deficient subjects who received the fortified beverage showed significant improvements in fitness (post-exercise reduction of heart rate) and cognitive performance (nonverbal mental ability score). The study showed that consumption of a multiple-micronutrient-fortified beverage for 16 weeks had significant effects on iron status, iodine status, physical fitness, and cognitive performance among iron- and/or iodine-deficient Filipino schoolchildren. Anthelmintic therapy improved iron status of anemic children and iodine status of the iron-adequate children at baseline but it had no effect on physical fitness and cognitive performance. The results from the clinical study showed that a multiple-micronutrient-fortified beverage could play an important role in preventing and controlling micronutrient deficiencies.

Key words: Children, fortified powder beverage, iodine, iron, multiple micronutrient

Introduction

Micronutrient malnutrition has been recognized not only to be widespread but also, if uncorrected, to cause serious health, developmental, and economic problems [1–4]. More than 2 billion people worldwide are affected by micronutrient malnutrition [1–4]. In addition, children in developing countries are prone to infection, including chronic infection with a variety of parasites [5–7]. The combined effects of undernourishment and chronic helminth infections can be serious. In areas where both are common, much of the student population may carry a significant health burden [2, 5–7], with resulting delays in physical, emotional, and intellectual growth that have the potential to prevent the children from reaching their full potential in both physical and mental development.

The nutrition status of children in developing countries reflects the fact that, for much of the world's population, adequate nutrition is hindered by a plethora of geopolitical, cultural, and economic issues [8, 9]. In fact, one of five people in developing countries does not regularly consume enough food to meet minimum nutrition requirements [9]. Deficiencies of iron, iodine, and vitamin A are considered important global health problems [1–4], due to both widespread prevalence and the potential for such nutritional deficits to create serious health problems [10]. Deficiencies of zinc [11] and folate [12] are also common. Vitamin

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C can be seasonally difficult to obtain in some regions [10], and in some groups, cultural practices restricting exposure to sunlight for female children create deficits of vitamin D [13].

Iron deficiency and anemia

The most widespread nutrition problem in the world is anemia [2–4, 14], affecting an estimated 2.15 billion people globally, with women and children affected the most. As much as 90% of anemia cases result directly from a deficiency of iron [14].

In children, anemia has been shown to affect both physical and cognitive development. Anemia produces pronounced lethargy with a decreased physical capacity for activity, which in children results in less time spent playing or exploring [1–4, 15–18]. Cognitive function is impaired in anemic schoolchildren, as evidenced by poorer school performance and lower scores on tests of concentration and cognitive development [16–20]. "Subclinical" iron deficiency is also recognized as a public health issue in schoolchildren. Non-anemic iron deficiency has been demonstrated to have subtle but demonstrably adverse health consequences, including lethargy, decreased physical capacity, decreased immune function, increased infection, and increased morbidity from infection [21, 22].

Iodine deficiency

Iodine deficiency, the single most preventable cause of mental retardation in the world, is another critical public health issue; approximately 40% of the world's population lives in areas where the risk of iodine deficiency disorder (IDD) is significant [23–25]. The prevalence of iodine deficiency is estimated to be approximately 250 million cases worldwide, with 50 million people suffering from goiter [26] and another 3.5 million affected by congenital IDD-associated cretinism [26, 27]. IDD causes neurologic abnormalities and impairment, with cognitive effects that range from mild motor or cognitive deficits to severe congenital or developmental retardation [25]. The impact of IDD on intelligence quotient (IQ) scores has been estimated at a decrease of 10–15% [24], or about 10 points [28].

Multiple micronutrient deficiencies

In developing countries, where people may be deficient in several micronutrients at one time, multiple-micronutrient supplementation may be necessary for optimal effect. In addition, many critical vitamins are interdependent with regard to efficacy and optimal absorption. Vitamin A is critical for iron metabolism and utilization; response to iron supplementation is measurably diminished if vitamin A deficiency is also present and is not simultaneously treated [29, 30].

Vitamin C is also necessary for optimal iron absorption [31, 32]. Deficiencies of vitamin A and iron, in turn, decrease thyroid metabolism, which subsequently decreases the response to supplemental iodine [27].

Intervention methods

Although long-term resolution of micronutrient deficiencies in the developing world will probably include educational programs and nutrition diversification [6], short-term urgency and practical considerations have favored two approaches to intervention. These include fortification of commonly consumed foods and supplementation [33].

Micronutrient supplementation has largely produced positive results with respect to growth and nutrition status [34–37]. A positive effect of iron supplementation on cognitive functions has been observed in schoolchildren, as well [16–18, 38–40]. Iron supplementation has been demonstrated to improve development and cognitive function in both anemic [41] and nonanemic iron-deficient schoolchildren [21]. Iodine supplementation has been shown to reverse the effects of IDD, with the exception of congenital retardation or severe early iodine deficiency [25, 42]. Zinc supplementation, as well, has been shown to improve growth and cognitive performance [34].

Although supplementation has been proven effective in resolving micronutrient deficiencies, logistical, cultural, and economic issues in field supplementation have hindered major progress in alleviating the public health problem that multiple micronutrient deficiencies represent in the developing world [43]. Recent efforts have focused on the fortification of common foods, an approach considered to be effective as well as very inexpensive [44–46].

Field efficacy trial in the Philippines

This study evaluated the effect of a multiple-micronutrient-fortified beverage on iron and iodine status and functional endpoints (fitness and mental abilities). Compliance (or acceptability of beverage) of subjects was assessed. The fruit-flavored beverage contained physiologic levels of 11 micronutrients, including iron, vitamin A, and iodine [46]. In addition, the fortified beverage utilized a fortification approach that delivers highly bioavailable micronutrients without changing the taste or appearance of the consumed final product [46].

Subjects

This study was a randomized, double-blind, placebo-controlled field efficacy trial that evaluated

a micronutrient-fortified dietary supplement in the presence or absence of anthelmintic therapy in schoolchildren in the Philippines. The proposal was given human subjects approval by the NCP ethical review committee, whose members include representatives from Helen Keller International (Philippines) and United Nations Children's Fund (UNICEF). A total of 851 children in grades 1–6 were enrolled and 808 were subsequently evaluated. Children were recruited from four elementary schools in the municipality of Balete, located in the province of Batangas in the Philippines. Selection of participating schools considered the prevalence of both macronutrient and micronutrient deficiencies. Overall prevalence of moderate-to-severe malnutrition in this district's schools is 25%. Written consent from the parent or guardian was obtained for all students enrolled. The actual intervention and assessment of nutrition status were conducted from October 1998 to March 1999.

Research design

Study participants were assigned, through randomization at the individual level, to one of four different treatment groups. This provided at least 200 subjects per treatment group, yielding at least 80% power in detecting small effects for fortified beverage and/or albendazole at $\alpha = 0.05$. The sample size computation was generated using the Power Analysis and Sample Size version 1.0 program developed by Hintze [47]. Subsamples of the total groups were selected for urinary iodine excretion (UIE) level determination, dietary assessment, and a socioeconomic survey. For UIE determination, 320 subjects/group were required for 80% power to detect a difference of 10 at $\alpha = 0.05$. For the socioeconomic and dietary assessments, a subsample of 200 children was selected. Both the researchers and the study participants were blinded to the treatment assignment of each child. The delivery of the intervention was strictly supervised and observed by field assistants to prevent contamination or sharing of the beverage.

The study design is shown in figure 1. Group 1 received fortified beverage with anthelmintic therapy; group 2 received fortified beverage with placebo anthelmintic therapy; group 3 received nonfortified beverage with anthelmintic therapy; and group 4 received nonfortified beverage with placebo anthelmintic therapy. Each study subject received a 200-ml serving of either fortified or nonfortified beverage twice each school day for a total of 16 weeks. A single serving (25 g sachets) contained iron (4.8 mg), vitamin A (700 IU), iodine (48 μg), zinc (3.75 mg), vitamin C (75 mg), riboflavin (0.46 mg), folic acid (0.06 mg), vitamin B_{12} (0.5 μg), vitamin B_6 (0.5 mg), vitamin E (2.5 mg), and niacin (2.5 mg) (see box 1). Anthelmintic treatment consisted of one 400-mg albendazole tablet given at the start and end of the intervention. Placebo beverage and placebo anthelmintic pills were indistinguishable from their counterparts in appearance, smell, and taste.

Methods

Assessments of overall health and nutrition status as well as a 3-day recall of dietary intake were obtained both at baseline and immediately post-intervention. The general health of study subjects was evaluated through a physical exam and a medical history. Children with a hemoglobin level ≤ 8 g/dl were treated and excluded from the study.

Anthropometric assessments included weight, height, and analysis of nutrition status using the Epi Info version 6 software (Epidemiology Program Office, Center for Disease Control and Prevention, US Department of Health and Human Services). Hemoglobin was instantly measured using the HemoCue® kit (Hemocue AB, Angelholm, Sweden). UIE was determined from urine samples, immediately transferred to cryovials that were sealed, stored at –20° C, and submitted to the Philippine Food and Nutrition Research Institute for iodine content analysis using the perchloric method.

Stool specimens were collected at baseline, 3 weeks after the deworming was given, and again at the end of intervention. Quantitative stool examination was done using the Kato-Katz technique [48]. Slides were prepared and counted for hookworm eggs in the field laboratory; egg counts for *Ascaris lumbricoides* and *Trichuris trichiura* eggs were performed at both the field and the central laboratory.
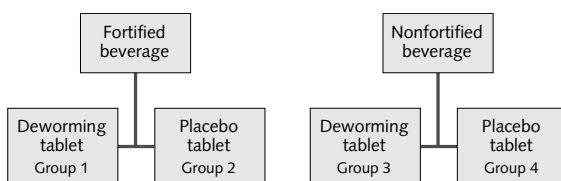
FIG. 1. Clinical study design

BOX 1. Contents of single serving (25 g)	
Iron	4.8 mg
Vitamin A	700 IU
Iodine	48 μg
Zinc	3.75 mg
Vitamin C	75 mg
Riboflavin	0.46 mg
Folic acid	0.06 mg
Vitamin B_{12}	0.5 μg
Vitamin B_6	0.5 mg
Vitamin E	2.5 mg
Niacin	2.5 mg

Physical fitness was assessed using a modification of the Harvard step test by Montoye for cardiovascular endurance of different age groups [49] and pushups for muscular endurance [50]. This modification of the Harvard step test did not require additional weight load (per kg of body weight) but it varied step height per age. Auscultation of the chest for heart rate measurement was done by trained research staff. Heart rate was taken at rest, immediately after exercise, and at four 1-minute intervals post-exercise. Resting heart rate was taken only after the subject had remained seated for 5 minutes. Each subject was assigned a research staff member who took both baseline and endline measurements. The duration of the step test was maintained at 3 minutes (180 seconds). The frequency of the steps was set at 24 cycles/minute and the cadence maintained by a metronome amplified through an audio system. The height of the step was adjusted according to the height of the child. Children were given detailed instructions and were allowed to practice before the actual test was performed. Heart rates recorded during recovery were analyzed at each time point as well as through a fitness index score, which was equal to the duration of the test (180 seconds) divided by the sum of heart rates for the 5-minute recovery period. A random sub-sample of boys aged 8–12 years also performed standard pushups and the number of properly performed pushups were observed and recorded by trained research staff.

Cognitive ability was measured using a standardized written mental-abilities test called the Primary Mental Abilities Test for Filipino Children (PMAT-FC), developed by Dr. Nelia T. Vargas-Benito in 1993. The test measures the following three basic mental abilities: verbal, nonverbal, and quantitative. Specifically, the test covers general knowledge and comprehension, verbal relationships, fundamental mathematical comprehension and skills, numerical sequencing, and ability to perceive and apply relationships based on meaningless stimuli. First-grade students were tested individually by an interview with a test administrator. Grade 2 students were tested as a group but a test administrator read aloud the test questions to assist students without true reading proficiency. Children in grades 3 through 6 were tested as a group and students read and answered questions on their own.

For quantitative variables, means and standard deviations were calculated for each treatment group and by combining groups 1 and 2 for the fortified group and groups 3 and 4 as the nonfortified group (fig. 1). Analysis of variance (ANOVA) was performed to test for differences of the means among the treatment groups. If the F-test from the ANOVA was significant, a multiple range test was done to identify which pairwise comparison of means was significant. Further analyses were conducted on different subsets of subjects who were grouped based on hemoglobin and/or UIE levels at baseline. The subset analyses were carried out because treatment effects of supplementation have been demonstrated to be more visible among subjects who are micronutrient deficient at baseline [17, 35, 46, 51, 52]. Subset analyses, therefore, identified groups of individuals more likely to benefit from the intervention.

Results

The nutrition profile at baseline of the subjects enrolled in this study largely mirrored the findings of the national survey conducted in 1998. Of the 808 elementary students evaluated, 52% (419 subjects) were anemic (hemoglobin < 12 g/dl). Five percent of all students were severely anemic (hemoglobin levels > 8 to < 10 g/dl) and about 21% were moderately to severely anemic (hemoglobin < 11 g/dl). The children from whom endline hemoglobin data were unavailable are evenly distributed across the four treatment groups. There was no significant difference in the hemoglobin level of the children across treatment groups at baseline. Approximately 90% of all the students evaluated were iodine deficient (UIE ≤ 100 µg/L), with 35% measured as severely deficient (UIE < 20 µg/L).

There were no significant differences between treatment groups with regard to age, socioeconomic demographic characteristics, 24-hr typical dietary intake, or any anthropometric measurement (table 1). Overall, 54% (369/677) of all subjects had at least one type of helminth infection and most of the infections were calculated to be of light intensity. A total of 290 (43%), 150 (22%), and 74 (11%) were positive for *Ascaris, Trichuris*, and hookworm respectively. There was no significant difference in the cumulative prevalence, prevalence of mixed infections, and the prevalence of *Ascaris, Trichuris,* and hookworm infection among the four treatment groups. There were no significant differences between treatment groups with regard to compliance or acceptance of the beverage; 95.9% of children who received fortified beverage liked the beverage as much or more than the juice they typically drank at home (versus 96.3% of children who drank placebo beverage). Among non-anemic subjects, the group receiving fortified beverage had a slightly lower baseline UIE level than those in the placebo group (37.00 versus 47.89 µg/L, respectively, $p = .035$). No other significant differences between treatment groups in any baseline biochemical analysis were observed. There were also no differences observed between groups with regard to baseline cognitive function, physical fitness, or general medical history.

Anthropometric status

Analysis of the children's anthropometric status at post-intervention revealed that there was a slight increase in weight and height for all four treatment groups (table 2). When the children were grouped

TABLE 1. Characteristics of study participants at baseline by treatment group

Variable	Treatment group				
	Fortified, dewormed	Fortified, not dewormed	Nonfortified, dewormed	Nonfortified, not dewormed	*P*-value
n	203	209	213	206	
Age [a]	10.1 ± 2.1	9.8 ± 2.1	9.9 ± 2.2	9.9 ± 2.3	.37
% Male	53.7	49.8	53.5	51.9	.84
Anthropometric status					
n	203	209	213	206	
Weight (kg) [b]	24.59 ± 6.07	24.27 ± 6.60	24.52 ± 6.75	24.23 ± 6.69	.93
Height (cm) [b]	127.19 ± 11.65	126.04 ± 12.08	126.71 ± 11.95	125.99 ± 12.18	.70
Weight-for-age z-score [b, c]	−1.70 ± 0.78	−1.60 ± 0.71	−1.65 ± 0.70	−1.70 ± 0.71	.46
Height-for-age z-score [b, c]	−1.85 ± 0.93	−1.72 ± 0.97	−1.76 ± 0.89	−1.83 ± 0.88	.40
Weight-for-height z-score [b, c, d]	3.75 ± 5.29	3.23 ± 5.26	3.47 ± 5.31	3.41 ± 5.29	.97
Iron status					
n	196	200	207	205	
Hemoglobin level (g/dl) [b]	11.91 ± 1.33	11.86 ± 1.25	11.93 ± 1.23	11.92 ± 1.23	.95
% Non-anemic (Hb ≥ 12 g/dl)	44.9	48.5	50.7	48.3	.71
% Iron-deficient					
Hb ≥11 to <12 g/dl	33.7	29.0	29.0	33.2	.60
Hb <11 g/dl	21.4	22.5	20.3	18.5	.79
Iodine status					
n	136	156	156	163	
Urinary iodine level (µg/L) [b]	40.82 ± 42.19	41.08 ± 40.07	46.14 ± 46.47	48.33 ± 48.38	.36
% Non-iodine deficient (UIE ≥ 100 µg/L)	8.8	9.6	12.8	11.0	.69
% Iodine-deficient					
UIE ≥ 50 µg/L to < 100 µg/L	17.6	19.2	19.9	23.9	.56
UIE ≥ 20 µg/L to < 50 µg/L	40.4	34.0	28.8	34.4	.23
UIE < 20 µg/L	33.1	37.2	38.5	30.7	.44
Physical fitness					
n	181	186	186	194	
Fitness index score [b]	62.13 ± 9.93	61.32 ± 9.87	63.56 ± 10.04	62.98 ± 9.35	.13
Push-up capacity [b, e]	6.38 ± 4.10	5.44 ± 2.20	6.44 ± 3.77	6.25 ± 3.56	.71
Cognitive performance					
n	186	185	188	183	
Verbal ability score [b]	7.56 ± 4.28	7.33 ± 4.20	8.10 ± 3.96	7.45 ± 4.35	.30
Non-verbal ability score [b]	2.65 ± 1.54	2.55 ± 1.58	2.63 ± 1.50	2.73 ± 1.50	.73
Quantitative ability score [b]	7.67 ± 2.84	7.36 ± 3.31	7.68 ± 3.24	7.22 ± 3.05	.40
Total score [b]	17.88 ± 6.83	17.24 ± 7.37	18.41 ± 7.13	17.37 ± 7.18	.37
Parasitic infection prevalence (%)					
n	159	172	175	171	
Ascaris	40	46	43	42	.70
Trichuris	24	25	17	23	.30
Hookworm	13	15	7	9	.10
Cumulative	55	58	53	53	.70
Mixed	21	23	14	19	.14

a. Values are means ± SD.
b. Values are means ± SE.
c. Z-scores were computed based on the NCHS standards.
d. Sample size for the groups was 119, 131, 129, and 126, respectively.
e. Sample size for the groups was 29, 25, 32, and 28, respectively.

by type of beverage received, regardless of deworming treatment, those given the fortified beverage had slightly higher increases in weight and height than did the children given the nonfortified beverage. When analyzed according to deworming group, those who received the deworming tablet were found to have a slightly higher increase in weight. However, the differences observed in all these instances were not statistically significant.

Anemia and iodine deficiency

At baseline, most subjects (52%) were anemic. The consumption of the fortified beverage had no significant effect on iron status when hemoglobin levels of < 12 g/dl was used as a cutoff. However, a significant improvement in iron status was demonstrated among the subjects who had hemoglobin levels < 11 g/dl at baseline. An analysis of the changes in iron status relative to the severity of anemia at baseline revealed a strong association between the efficacy of the fortified beverage and the severity of anemia at baseline (table 3). The highest increase in hemoglobin level was obtained in the subgroup that had < 10 g/dl hemoglobin level at baseline, even though the difference was not significant

($p < .10$). By contrast, the subjects who had adequate iron status (≥ 12 g/dl hemoglobin) at baseline showed a slight reduction in hemoglobin level. The correlation between baseline hemoglobin level and the effect of the fortified beverage on iron status was highly significant ($p < .0001$). The number of children who remained moderately or severely anemic at the end of the 16-week intervention period was also significantly lower among children who received the fortified beverage (14.9% versus 28.75%, respectively, $p = .03$) (results not shown). The benefit of the fortified product on iron status is similar to that of deworming. Deworming significantly improved the iron status of moderately to severely anemic subjects at baseline, (12.04 g/dl in dewormed children versus 11.6 g/dl in children not dewormed, $p = .02$) (results not shown).

Children who consumed the fortified beverage showed dramatic improvement in iodine status (table 4). In children who received the fortified product, the median UIE level increased from 41.31 µg/L at baseline to 67.98 µg/L after the 16-week intervention. Among those who received the placebo beverage, the median UIE level reduced significantly from 46.99 µg/L at baseline to 39.74 µg/L after intervention. The increase in UIE level after supplementation is strongly associated with iodine status at baseline. Subjects who were iodine replete at baseline (≥ 100 µg/L) experienced a significant drop in UIE level at

TABLE 2. Effect of the fortified beverage on anthropometric status

| Variable | Treatment Group | | P-value |
	Fortified	Nonfortified	
n	412	419	
Weight (kg)[a]			
Baseline	24.66 ± 0.20	24.68 ± 0.20	.95
Post-intervention	26.16 ± 0.22	26.15 ± 0.22	.97
Change	1.50 ± 0.05	1.47 ± 0.05	.69
Height (cm)[a]			
Baseline	126.89 ± 0.33	126.99 ± 0.33	.83
Post-intervention	129.22 ± 0.34	129.29 ± 0.34	.88
Change	2.33 ± 0.04	2.30 ± 0.04	.64
Weight-for-age z-score[a]			
Baseline	−1.63 ± 0.04	−1.66 ± 0.04	.62
Post-intervention	−1.52 ± 0.04	−1.54 ± 0.04	.66
Change	0.12 ± 0.01	0.12 ± 0.01	.91
Height-for-age z-score[a]			
Baseline	−1.77 ± 0.05	−1.78 ± 0.05	.84
Post-intervention	−1.69 ± 0.05	−1.71 ± 0.05	.81
Change	0.08 ± 0.01	0.08 ± 0.01	.73
Weight-for-height z-score[a, b]			
Baseline	−0.75 ± 0.13	−0.82 ± 0.14	.31
Post-intervention	−0.69 ± 0.14	−0.74 ± 0.14	.57
Change	0.05 ± 0.05	0.07 ± 0.05	.52

a. Values are adjusted means ± SE.
b. Sample size for the groups was 231 and 236, respectively.

TABLE 3. Effect of fortified beverage on iron status (hemoglobin g/dl ± SE)

| Evaluation | Treatment Group | | P-value |
	Fortified	Nonfortified	
All subjects ($n = 809$)			
Baseline	11.90 ± 0.06	11.95 ± 0.06	.58
Post-intervention	12.19 ± 0.06	12.16 ± 0.06	.72
Change	0.29 ± 0.08	0.21 ± 0.08	.47
Hb < 10g/dl at baseline ($n = 44$)			
Baseline	9.33 ± 0.12	9.42 ± 0.13	.55
Post-intervention	11.91 ± 0.33	11.14 ± 0.38	.10
Change	2.58 ± 0.35	1.72 ± 0.40	.08
Hb < 11g/dl at baseline ($n = 167$)			
Baseline	10.24 ± 0.07	10.25 ± 0.08	.93
Post-intervention	12.01 ± 0.14	11.63 ± 0.15	.05
Change	1.72 ± 0.15	1.35 ± 0.16	.09
Hb < 12 g/dl at baseline ($n = 419$)			
Baseline	11.00 ± 0.05	11.01 ± 0.05	.89
Post-intervention	12.02 ± 0.08	11.85 ± 0.08	.15
Change	1.02 ± 0.09	0.85 ± 0.09	.18
Hb ≥ 12 g/dl at baseline ($n = 390$)			
Baseline	12.89 ± 0.06	12.86 ± 0.06	.69
Post-intervention	12.35 ± 0.09	12.46 ± 0.09	.40
Change	−0.54 ± 0.11	−0.40 ± 0.10	.35

post-intervention, whereas the highest improvement in iodine status was observed in subjects who had UIE levels below 20 µg/L. The data suggest that the bioavailability of iodine is tightly regulated by the iodine status of the subjects at baseline. Regression analysis showed there is a significant ($p < .0001$) correlation between improvement in iodine status and baseline iodine status. Although it is not as dramatic as that of the fortified beverage, it is interesting to note that anthelmintic treatment had some effect on iodine status at post-intervention ($p < .07$) In fact, among subjects with baseline hemoglobin levels ≥ 12 g/dl, the increase in UIE level among the dewormed (21.7 µg/L) was significantly higher than that of the placebo group (5.98 µg/L) (results not shown). Although preliminary, the data suggest that there is a positive interaction of baseline iron status and anthelmintic treatment on iodine status.

The interaction between iron and iodine status on both iron and iodine status at the end of the intervention was also evaluated by using a regression analysis (not shown). There was no correlation between iodine status at baseline and iron status at post-intervention ($p = .92$). The effect of baseline hemoglobin level on change in iodine status seems to show some correlation ($p = .18$). The subjects with hemoglobin levels ≥ 11 to < 12 g/dl at baseline had significantly ($p < .01$) less post-intervention increase in UIE levels than did those

with hemoglobin levels > 12 g/dl at baseline (results not shown).

Physical fitness

The effect of the fortified beverage on changes in heart rate was dramatic and consistent. The fortified beverage consistently showed beneficial effect in reducing post-exercise heart rates (table 5). Significant difference in changes in heart rate was consistently observed among the subjects with hemoglobin levels < 12 g/dl and hemoglobin levels < 12 g/dl and UIE levels < 50 µg/L at the baseline. Interestingly, the fortified beverage also showed significant and more dramatic effect in reducing heart rate among the children with hemoglobin levels > 12 g/dl and UIE levels > 20 to < 50 µg/L, hemoglobin levels > 12 g/dl and UIE levels > 50 to < 100 µg/L, and UIE levels > 20 to < 50 µg/L at baseline (table 5).

The increases in fitness index scores in the subjects who received the fortified and nonfortified beverage were 1.25 and 0.29, respectively. Although the score is higher in the treated subjects than in the placebo group, it was not significant ($p = .11$). It is likely that the difference observed is due to the fortified beverage, because the anthelmintic-treated subjects had lower increases in fitness index scores compared with the untreated group (dewormed = 0.53, placebo = 0.10; $p =$

TABLE 4. Effect of fortified beverage on iodine status (UIE level µg/L ± SE)

| Evaluation | Treatment Group | | P-value |
	Fortified	Nonfortified	
All subjects ($n = 611$)			
Baseline	41.31 ± 2.56	46.99 ± 2.45	.11
Post-intervention	67.98 ± 2.70	39.74 ± 2.58	< .0001
Change	26.68 ± 3.44	−7.25 ± 3.29	< .0001
UIE < 20 µg/L at baseline ($n = 226$)			
Baseline	11.12 ± 0.55	11.71 ± 0.55	.43
Post-intervention	60.69 ± 3.77	27.77 ± 3.73	< .0001
Change	49.57 ± 3.76	16.06 ± 3.72	< .0001
UIE ≥ 20 to < 50 µg/l at baseline ($n = 199$)			
Baseline	31.78 ± 0.86	33.55 ± 0.91	.15
Post-intervention	70.23 ± 4.86	45.05 ± 5.16	< .0001
Change	38.44 ± 4.85	11.49 ± 5.14	< .0001
UIE ≥ 50 to < 100µg/l at baseline ($n = 122$)			
Baseline	70.14 ± 2.04	67.96 ± 1.77	.42
Post-intervention	82.86 ± 6.58	55.9 ± 5.7	.002
Change	12.72 ± 6.78	−12.06 ± 5.88	.006
UIE ≥ 100 µg/l at baseline ($n = 64$)			
Baseline	148.53 ± 9.77	153.90 ± 8.64	.64
Post-intervention	83.88 ± 9.56	56.4 ± 8.45	.02
Change	−64.65 ± 13.95	−97.50 ± 12.33	.05

TABLE 5. Effect of fortified beverage on changes in heart rates (bpm ± SE)

| Time after exercise | Treatment Group | | P-value |
	Fortified	Nonfortified	
All subjects ($n = 742$)			
1 minute	−2.91 ± 0.76	−1.19 ± 0.75	.11
2 minutes	−2.29 ± 0.71	−0.41 ± 0.70	.06
3 minutes	−2.19 ± 0.67	−0.65 ± 0.67	.10
4 minutes	−1.98 ± 0.64	−0.53 ± 0.63	.11
Hb < 12 g/dl ($n = 390$)			
1 minute	−1.65 ± 0.53	−0.24 ± 0.53	.06
2 minutes	−1.30 ± 0.51	0.17 ± 0.51	.04
3 minutes	−0.95 ± 0.48	0.24 ± 0.48	.07
4 minutes	−0.83 ± 0.44	0.10 ± 0.44	.13
Hb < 12 g/dl and UIE ≤ 50 µg/L ($n = 191$)			
1 minute	−2.08 ± 0.70	−0.25 ± 0.73	.06
2 minutes	−1.87 ± 0.71	−0.45 ± 0.74	.02
3 minutes	−1.47 ± 0.69	0.63 ± 0.72	.03
4 minutes	−0.88 ± 0.63	0.40 ± 0.65	.15
UIE ≥ 20 to < 50 µg/L ($n = 175$)			
1 minute	−3.64 ± 1.54	0.65 ± 1.60	.05
2 minutes	−2.78 ± 1.47	1.87 ± 1.54	.03
3 minutes	−3.63 ± 1.39	1.57 ± 1.46	.01
4 minutes	−3.05 ± 1.37	2.19 ± 1.43	.01

.44). It is important to note that deworming had either no effect or a negative effect on fitness index scores (data not shown). On the other hand, the effect of deworming on change in heart rate was inconclusive.

Cognitive performance

The effects of the fortified beverage on mental ability scores are presented in table 6. Consumption of fortified beverage showed no significant effect on changes in total cognitive score of all subjects. By contrast, the subjects who were both iron deficient (hemoglobin < 11 g/dl) and mildly iodine deficient (UIE > 50 to < 100 μg/L) at baseline showed significant increases in changes of total cognitive ($p < .02$), nonverbal ability ($p < .03$), and verbal ability ($p < .02$) scores.

Among subjects who were moderately to severely anemic (hemoglobin < 11 g/dl) at baseline, children receiving the fortified beverage showed significant improvement in changes in nonverbal ability score ($p < .05$). The iron-deficiency-anemia-mediated impact of the fortified beverage on verbal ability scores was enhanced to some extent by iodine deficiency (table 6). Changes in quantitative scores were inconsistent; the effect of fortified beverage on quantitative scores is inconclusive (data not shown). Improvement in mental ability scores is specific to the fortified beverage, because anthelmintic treatment showed either no effect or had a negative effect (data not shown).

Discussion

Baseline data demonstrate that both iron and iodine deficiencies are prevalent among Filipino schoolchildren. At baseline, 52% and 21% were anemic, using Hb levels of < 12 g/dl and < 11 g/dl as cutoff points, respectively. Likewise, about 90% and 37% were iodine deficient at baseline, using UIE levels of < 100 μg/L and <20 μg/L as cutoff points, respectively. The prevalence of micronutrient deficiencies observed at baseline is higher than that observed in the 1998 Philippine national survey [48]. According to this relatively recent survey, anemia and iodine deficiency among schoolchildren are about 37% and 36%, respectively. A little over half of all children examined had at least one type of helminth infection, but most of those infected had light infections. This should be taken into account when interpreting the benefit of concomitant deworming and fortification.

Although it is well recognized that food fortification is among the preferred and cost-effective approaches in combating micronutrient malnutrition, its effectiveness in developing countries is yet to be demonstrated. One of the limiting factors is the lack of simple and affordable technology to fortify foods with stable and bioavailable nutrients without compromising commonly accepted taste and appearance [46, 53, 54]. In fact, compliance has been identified as one of the key limiting factors in combating micronutrient malnutrition through supplementation [55]. The results showed that the fortification of the powder fruit drink with multiple micronutrients (three minerals and eight vitamins) had no significant impact on the amount of beverage consumed and overall compliance. When asked to compare the fortified beverage with the juice they usually drink at home, 20% of the children liked the beverage better and 76% showed no preference, with only 4% preferring juice.

This randomized, double-blind, placebo-controlled study showed that repeated consumption of the fortified beverage has a significant impact on improving the iron status of the subjects with hemoglobin levels < 11 g/dl at baseline. The data suggest that utilization of iron from the fortified beverage is highly regulated by the iron status of the subjects. The highest increase

TABLE 6. Effect of fortified beverage on changes in mental ability scores

Nutrition status at baseline	n	Treatment Group		P-value
		Fortified	Nonfortified	
Change in cognitive score				
All	742	1.82 ± 0.22	1.66 ± 0.22	.62
Hb < 11 g/dl and UIE > 50 to < 100μg/L	24	5.29 ± 1.74	0.42 ± 1.31	.02
Change in nonverbal-ability score				
All	742	0.21 ± 0.10	0.18 ± 0.10	.84
Hb < 11 g/dl	144	0.50 ± 0.23	−0.07 ± 0.25	.08
Hb < 11 g/dl and UIE ≤ 20 μg/L	44	1.37 ± 0.50	0.09 ± 0.50	.06
Hb < 11 g/dl and UIE ≤100 μg/L	101	0.82 ± 0.27	−0.04 ± 0.30	.03
Hb < 11 g/dl and UIE > 50 to ≤ 100 μg/L	24	2.08 ± 0.81	−0.18 ± 0.61	.03
Change in verbal-ability score				
All	742	0.76 ± 0.14	0.60 ± 0.14	.42
Hb < 11 g/dl and UIE > 50 to < 100 μg/L	24	1.05 ± 0.83	−1.3 ± 0.62	.02

was obtained in the subjects with hemoglobin levels < 10 g/dl at baseline (table 3). Regression analysis also showed that the increases in hemoglobin levels at post-intervention were significantly correlated with baseline iron status. This corroborates data obtained by others among Tanzanian schoolchildren with the same delivery system [33]. Note that the iron consumed daily in the study was not only at physiologic levels but also consumed only during the school days for 16 weeks.

There are few intervention studies with iron-fortified foods in schoolchildren [3, 33]. The effect of fortified biscuits on micronutrient status in schoolchildren in South Africa showed a decrease in hemoglobin levels after 6 months and a significant increase in hemoglobin levels after 12 months of intervention [3]. Many of the other iron intervention studies in schoolchildren use supplementation at pharmaceutical doses [17, 35, 37]. In these studies, significant changes in iron status were observed only among the anemic subjects [17, 35].

Repeated consumption of the multiple-micro-nutrient-fortified beverage by Filipino schoolchildren resulted in significant improvement in iodine status (table 4). The highest increase in UIE level was obtained among the subjects who were severely iodine deficient (UIE < 20 μg/L) at baseline. By contrast, a decrease in UIE levels was observed among those who were iodine adequate (UIE > 100 μg/L) at baseline. Furthermore, the results demonstrate that the utilization of iodine from the fortified product is tightly regulated. Regression analysis showed that baseline iodine status is negatively correlated with change in UIE levels at the end of the study. No interaction was observed between iodine status at baseline and increases in hemoglobin levels at post-intervention. However, although the association between iron status at baseline and post-intervention change in UIE level was nonsignificant, the subjects who were iron adequate at baseline had a significantly higher increase in UIE levels than those who had baseline hemoglobin levels between 11 and 12 g/dl. Note, however, that the increase in UIE levels observed among the subjects who were iron deficient (hemoglobin < 11 g/dl) at baseline was not significantly different from that in subjects who were iron adequate (hemoglobin > 12 g/dl) and mildly anemic (hemoglobin ≥11 g/dl to < 12 g/dl) at baseline.

Very few studies on the interaction between iron and iodine status have been reported in the literature. According to Zimmermann, et al. [27] the effect of iodine supplementation is impaired in goitrous children with iron-deficiency anemia. Furthermore, results from an iron supplementation study showed efficacy of iodized salt in goitrous children to be significantly improved by iron treatment [56]. It is possible that the marked improvement in iodine status observed in children consuming the fortified beverage could be due to the delivery of both iron and iodine through a single product.

Multiple studies have shown that micronutrient malnutrition, particularly of iron and iodine, has negative effects on growth, strength, mental development, and learning [15–20, 32–42]. Our results showed that the fortified beverage had no effect on growth of the schoolchildren. Limited studies have shown significant effect of iron supplementation on growth in schoolchildren [35, 37, 57]. However, these studies used pharmaceutical doses of iron in anemic subjects. A recent study by Latham et al. [33], however, did find a significant effect on growth (height and weight gain) and body mass index after repeated consumption of a fortified beverage after 6 months. It is likely that the lack of positive response observed in the Filipino study could be due to the short duration of the intervention phase (4 months).

Several clinical studies of iron supplementation in Guatemala [12, 58], Sri Lanka [14, 16, 17, 59], Indonesia [60], and Africa [63] have demonstrated a strong relationship between increased hemoglobin levels and common work performance capacity indicators, such as work productivity, heart rate, blood lactate, and oxygen intake. All of these studies used iron supplements instead of fortified foods, and none studied schoolchildren. The effect of the fortified beverage, even though the nutrients are consumed daily at physiologic levels, is interesting. The increase in the fitness index score of the subjects who received the fortified beverage was higher, even though it was not significant ($p < .11$), than in those who received the nonfortified beverage. The average change in heart rate as a function of time after exercise was consistently lower among those in the fortified group than in the nonfortified group (table 5). However, it reached significance only at 2 minutes after exercise ($p < .06$). Among subjects with hemoglobin levels < 12 g/dl at baseline, reduction in heart rate of those in the fortified group was significantly higher than in the nonfortified group at 1 and 2 minutes. There is an indication that iodine status may have an adverse effect on fitness in schoolchildren. Among the subjects who were moderately iodine deficient (UIE > 20 to < 50 μg/L) at baseline, those who received fortified beverage had significantly higher reduction in heart rate at 1, 2, 3, and 4 minutes after exercise. It is unclear why this particular group consistently responded positively to the fortified beverage by showing significantly increasing fitness as indicated by reduction of heart rate. It is likely that the level of iodine (96 μg) consumed per day and the duration of the study (4 months) were not adequate to provide benefits to those with UIE levels < 20 μg/L at baseline. By contrast, the group with baseline UIE levels > 50 μg/L probably already had adequate amounts of iodine, which were not affected by the fortified beverage.

Several studies of infants, preschool children, and schoolchildren have shown that iron-deficient subjects

had lower cognitive development and school performance [5, 16–32, 38–41]. In infants, iron supplementation was effective in improving iron status but not in correcting mental development deficit [19, 20]. Significant improvement in cognitive performance by iron supplementation in preschool and schoolchildren has been observed in Indonesia [17, 38, 61], India [39], and the United States [21, 22]. Unlike the study reported here, these studies used pharmaceutical doses of iron. Also, positive cognitive benefits were observed only in the subjects who were iron deficient at baseline.

Very limited studies have assessed the impact of iodine supplementation on cognitive performance in preschool and schoolchildren. In a controlled study done in Bolivia, improvement in IQ was demonstrated in all those schoolchildren who showed significant reduction in goiter [62]. Recently, results from a 1-year intervention study among iodine-deficient schoolchildren showed a significant improvement in mental performance among those children with increased UIE levels [42]. Our data demonstrate that consumption of a fortified beverage had a significant effect on nonverbal ability scores among subjects who were moderately to severely anemic (hemoglobin < 11 g/dl). Interestingly, the subjects who were both iron deficient (hemoglobin < 11 g/dl) and mildly iodine deficient (UIE > 50 to < 100 µg/L) at baseline had significantly increased total cognitive, nonverbal ability, and verbal ability scores.

Overall our results are consistent with results reported by others [17, 22, 38, 39, 61]. The significant cognitive benefits of the fortified beverage occurred only among subjects who were either anemic or both anemic and iodine deficient at baseline. Also, our results support the recently published data by Stoltzfus et al. [5], in which a physiologic level of iron supplementation for 1 year had a significant benefit on language and motor development among anemic preschool children. The effect of iron supplementation was limited to children with more severe anemia (hemoglobin < 8 g/dl) at baseline. Data published thus far, including ours, are consistent with the conclusion made by Sternberg et al. [26] that inadequate levels of vitamins and minerals in the blood reduces intellectual performance below a child's optimal level. Vitamins and minerals, in addition to a child's standard diet, seem to be particularly associated with a rise in nonverbal cognitive performance.

Conclusion

Our results show that daily delivery of multiple micronutrients including iron and iodine (at physiologic levels) via a commonly accepted powder fruit drink showed a significant effect on iron and iodine status. The utilization of both iron and iodine is highly regulated. Only the subjects who were deficient at baseline showed an increase in either hemoglobin or UIE levels. In addition, the repeated consumption of the fortified powder drink had a significant benefit in improving physical fitness (indicated by reduction in heart rate) and mental ability (indicated by nonverbal and verbal ability scores). Again, these functional benefits were obtained among subjects who were either iron and/or iodine deficient.

Acknowledgment

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Drinking to their health: Social analysis of a micronutrient-fortified beverage field trial

Martin Benjamin and Deborah M. Ash

Abstract

Anthropologic research was conducted among pregnant and lactating women in rural Tanzania in conjunction with clinical trials of a micronutrient-fortified beverage. Use of the beverage was examined through interviews and ethnographic observation in clinics and at home. Women liked the taste of the beverage, considered it beneficial to their health, preferred it to pills or injections, and most were willing and able to use it according to instructions. Most consumed the beverage according to schedule in the hope of improving pregnancy outcomes. However, public health facilities in Tanzania are not currently equipped to ensure regular delivery of micronutrient supplements, and many of the women with the worst nutrition profiles are also those who would be least able to purchase supplements on the open market. Successful distribution of micronutrient supplements in forms that appeal to consumers, such as a fortified beverage, will require programmatic attention to locally appropriate social marketing and to the challenges of reaching those with extremely low incomes.

Key words: Compliance, fortified beverage, medical anthropology, micronutrient malnutrition, product acceptance, social analysis

Research objectives

This paper discusses the anthropologic component of a micronutrient-fortified beverage field trial in Mpwapwa, Tanzania [1], which was conducted in association with clinical trials detailed elsewhere in this supplement [2] (see Box 1). The United Nations Children's Fund (UNICEF) funded research conducted in 1999 and 2000, in close cooperation with nutritionists and technicians from Cornell University (Ithaca, New York) and the Tanzania Food and Nutrition Centre (TFNC), during the clinical-trial period with expectant and nursing mothers. The anthropologic component was initiated to determine how such a beverage or similar micronutrient package would be accepted and consumed if clinical data indicated the program should go to scale. Among the study objectives, we sought to learn from and avoid common development pitfalls, investigate social reaction to the micronutrient beverage, and investigate potential obstacles to widespread distribution of such a product in East Africa.

In designing the study we sought to make recommendations that would be both practical and pos-

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Mention of names of firms and commercial products does not imply endorsement by the United Nations University.

BOX 1. Efficacy trial of a micronutrient dietary supplement in pregnant women in Tanzania

Food technologists at The Procter & Gamble Co. (P&G) produced both the micronutrient-fortified beverage mix and an identical tasting and looking nonfortified beverage mix, which served as the experimental and placebo treatments respectively. For the pregnancy study, two types of sachets were used with one colored green and labeled "G" and the other colored blue and labeled "H." Neither the researchers nor the study participants were aware of the identity of the package contents. The composition of the supplement in each sachet had been agreed to after extensive consultation by nutritionists at Cornell University, Tanzania Food and Nutrition Centre (TFNC), Micronutrient Initiative (MI), United Nations Children's Fund (UNICEF), and P&G and is further detailed by Latham and others elsewhere in this volume.

Sources: Ash et al. [1], Makola et al. [2].

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sible for the intended beneficiaries. Examples of well-intentioned projects gone awry abound in international health and development activities. However, when projects incorporate social scientific analysis into their structure, efforts to introduce and encourage beneficial but unfamiliar activities have an increased likelihood of being effective.

The social science component of the current research was intended to raise questions about the viability of introducing a multiple-micronutrient–fortified beverage into poor areas in ways that might reach the mothers and children with the worst nutritional profiles. Research questions included the following: Did women find compelling reasons to use the beverage? Did they find ways to work it into their daily routines? Did they seek to share its potential benefits with their children? Did some sell the powder to raise cash? Did they have problems keeping the powder safe from pilfering? Did other household members help or hinder women's use of the beverage? Also, given all the other competing demands on impoverished consumers' time and resources, how might a market for such a product be encouraged? And, finally, what additional structural obstacles would need to be overcome in the health sector in order for widespread distribution to be a success?

Study design: applying anthropology to micronutrient research

With these questions in mind, an anthropologic research project was launched that looked very different from the clinical trials to which it was attached. The variables in subjects' lives that epidemiologic research seeks to control for are the very ones that anthropology seeks to highlight. Whereas clinical research relies on the collection of measurable physiologic data, anthropology investigates unquantifiable factors through discussion and observation. While epidemiologic research requires appropriate, often large, sample sizes to have the statistical power to make valid conclusions, anthropology in complex societies is at its best when it delves deeply into the lives of a relatively small sample of a larger population. When clinical studies prick and poke subjects for blood samples and parasite counts, anthropologic research tries to set subjects at ease so they will express thoughts that they would otherwise keep hidden from outsiders and authority figures. When conducted in tandem, we found these two very different types of research to be quite complementary.

The anthropologic study was designed to get people talking. We first met with most of the women immediately after their initial clinical screening, introducing them to the beverage while engaging them in friendly banter. In this way a relationship was established that

was followed with home visits in many cases. The home visits generally lasted 30–90 minutes. We conducted semi-structured interviews, meaning we made sure to discuss certain crucial topics centering around individual impressions of the beverage and circumstances of its use, while also allowing conversation to include topics ranging from life histories to breastfeeding and birth planning to household economics. We could not, given the time available, collect quantitative data that would enable us to say that, for example, "X" percent of women would purchase a micronutrient product at price point "Y." With these parameters in mind and by following accepted anthropologic methods of participant observation, we can say, however, that the information we gathered is broadly representative of families in Tanzania and, by extension, is relevant to much of eastern, central, and southern Africa.

At the same time that we were talking with women and their families about where the micronutrient beverage fit in their lives, we were also talking with health personnel and observing health service facilities. We did this because many health programs are based on the assumption that health services will be delivered in remote areas in ways that correspond closely with planners' intentions. By observing health services as they are actually available to a not atypical set of Tanzanians, we were able to identify some of the issues that will affect the logistics and supply side of micronutrient-supplement distribution in this part of the world, beyond the immediate questions of consumer acceptability uncovered by the work with study participants.

Key findings: favorable and cautionary

The key findings that most gratify the team that formulated the micronutrient beverage are that most women liked it, preferred it as a delivery vehicle over pills or injections, considered it beneficial to their health, and were willing and able to use it according to instructions. When viewed in conjunction with the physiologic data presented by Latham [3] and others [2], the findings present a strong argument for going forward with a micronutrient beverage in East Africa. There is a second set of findings that is equally important, though, and is somewhat cautionary. These findings center around the fact that the women and children with the worst nutrition profiles, who would therefore benefit most from a supplement like a micronutrient beverage, are also by and large the poorest, most politically marginal members of society who would be least able to afford any daily cost of purchasing such a product.

Though the specific social relations of poverty we found in this research are unique to East Africa, these findings will hold for much of the rest of the world and should therefore be a topic of serious consideration for

any public or private organization pursuing the distribution of such a product to poor consumers who are at risk of micronutrient deficiency.

Favorable findings

The first set of findings is clear. Women liked the beverage, and they and their families did all they could to ensure that they consumed it on a regular basis. While many studies of "compliance" find low adherence to tablet regimens [4], we found that 74% consumed between 75% and 100% of their beverage sachets (with a mean consumption in these top three quartiles of 110 out of 112 possible sachets) and 92% consumed at least one-half of their sachets (with a mean consumption in the top two-thirds of the bottom quartile of 83 out of 112 sachets, or 74%) (table 1).

Most women found the taste pleasant, mentioning that it is similar to a popular flavor of soda. Their reasons for drinking the beverage had little to do with a craving for orange-flavored drink mix, though. Rather, most responded to the suggestion by medical experts that the product could have health benefits for themselves and their babies.

Most of the women in the study were from households that relied on farm products, petty trade, and casual labor to bring in about $10 (US dollars) per month per person, to meet all household needs for food, medicine, education, clothing, and shelter. Within their families, most women had little power to direct household resources toward their health. Unmarried pregnant women, who were perceived to be "soiling" the household, had even less claim than most for family support. Many of the women, therefore, willingly accepted the beverage as something they could use to improve their health that did not require approval from family members with greater authority over resources.

Equally significant is that other family members also were eager for the pregnant women among them to use the product. Husbands, sisters, and mothers-in-law all helped protect the product for the pregnant women and made sure they drank the beverage according to the daily schedule and got their refills every 2 weeks.

Children are central to Tanzanian social life, and most adults were enthusiastic about having a product available that might help offspring survive pregnancy and infancy. In a country with an estimated infant mortality rate (IMR) of 99/1,000 live births [5], in which it is not uncommon for a woman to have only a few children reach adulthood from as many as a dozen pregnancies, both pregnant women and their families were eager to do what they could to shift the odds in their favor.

In local parlance, the beverage was discussed as something that could "increase blood." People agreed that certain foods could increase blood, including scarce foods like meat and sporadically available foods like dark leafy vegetables. (Parenthetically, we therefore recommend that any micronutrient supplement manufactured for the East African market be available in a dark purple formula.) Few families, though, normally made special efforts to use diet to increase the blood of pregnant women until very late in the pregnancy, just before the anticipated blood loss during delivery. The information we gave—that increasing blood early in pregnancy could help mother and baby and that increasing the blood of nursing women might improve the quality of the milk for the infant—was not part of local ethnomedical understandings prior to the study. However, when given this information, most people evaluated it and incorporated it into their models of physiologic processes.

Families were then eager to adopt the beverage for pregnant women, because it was a non-cumbersome way to achieve the revised goal of increasing the mother's blood during and after pregnancy. Similar information regarding health benefits for children would stimulate demand for feeding micronutrient supplements to children. Though understanding of diet and bodily processes will vary from place to place, thus making research about local health conceptions important before implementing micronutrient-supplement programs elsewhere, the central objectives of improving maternal and child health will be shared by many poor families worldwide.

Cautionary findings

The second, cautionary set of findings presents much more of a challenge to those who wish to promote micronutrient supplements. These findings will also vary in their particularities from place to place, but will present similar obstacles overall throughout the nonwealthy world. Chiefly, the public supply stream is often broken, and the main consumer base consists of those people least able to allocate the cash needed to support a private micronutrient-supplement industry. Health services and supplies are largely inadequate in Tanzania, as they are in impoverished areas from Peru to Haiti to

TABLE 1. Compliance of supplementation of two servings per day during the first 8 weeks of the study

Number of Packets[a]		Consumption[b] n/N (%)
Mean	Range	
0	0	2/318 (0.6%)
28	25–28	7/318 (2.2%)
55	44–56	15/318 (4.7%)
83	64–84	58/318 (18.2%)
110	86–114	236/318 (74.2%)

a. Number of sachets consumed during first 8 weeks of study is based on the number of empty packages returned during follow-up.
b. Proportion of mothers who consumed stated amount.

Indonesia—preventive health care is minimal where doctors are few, facilities are Spartan, and supplies are scarce even for emergency medicine. In a country like Tanzania where even free medical supplies—such as the iron-folate tablets that are supposed to be available for pregnant women—often do not reach their intended recipients, any model of public distribution of micronutrient supplements will need to confront aggressively the serious institutional and supply stream weaknesses that currently prevent women and children from accessing many of those public health services that are nominally available to them.

Additionally, when considering a private model of selling micronutrient supplements directly to consumers, we found that the best of intentions to purchase such a product will often crash against the realities of household economics in impoverished areas. A basic graph of supply and demand, drafted with rough figures, indicates a fundamental fact of economics—in a totally free market, some consumers will always be left out. In the case of micronutrient supplements, the people who can least afford the cost of the product are exactly the "target demographic" with whom we ought to be most concerned (figures 1 and 2).

When food is a daily struggle, as it is especially in female-headed households, supplements will necessarily be a lower priority than food or medicine. When women have restricted access to household income, as in many households with a strong patriarchal organization, it is difficult for them to make the independent decision to purchase supplements for themselves or their children. Among the 64% of women we tested with hemoglobin concentrations indicating moderate-to-severe anemia, many reported having resources available, either through their own small income or family decisions about household expenditures, to only eat nutrient-rich foods such as meat, eggs, or milk as seldom as once or twice a month. Even the staple diet,

maize meal and beans, can be difficult to afford during the leanest months. As much as mothers and children may like a fortified beverage or other micronutrient product, whether for flavor or for anticipated health benefits, a private company would face considerable obstacles in creating a viable business model selling to the poorest groups with the least nutritious diets.

Applying the lessons: research into action

What we found through anthropologic research with the women in the study and through evaluating their health-services environment is a substantial challenge. Women and children enjoy drinking a micronutrient-fortified beverage. Families with good information appreciate the importance of improving the health profiles of mothers and children through the regular use of micronutrient supplements, and appropriate social marketing can inspire them to go to great lengths to acquire them. However, public distribution of such supplements can become mired in existing inefficiencies, and private sales will often miss the most important markets—in effect, micronutrient supplementation programs risk resembling other well-intentioned programs that assume rather than analyze and address the situational realities of consumer demand.

Overcoming these challenges should be of central concern in discussing the future of public-private partnerships in micronutrient supplementation. By working together on the beverage, for example, The Procter & Gamble Co. (P&G), Micronutrient Initiative (MI), UNICEF, TFNC, and the Cornell team developed a product that appeals to consumers and is relatively inexpensive to produce. Other products might be even less expensive to produce, such as fortified mixes for the family cooking pot or nutrient pre-mixes that can be ground into staple foods at the community grain mill. Careful social science research can establish whether
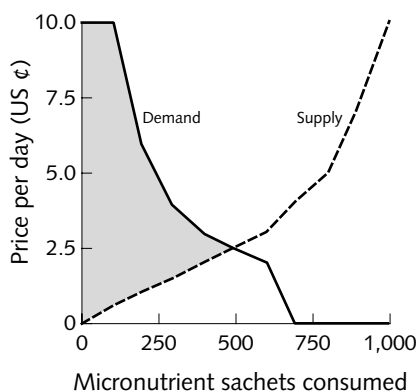

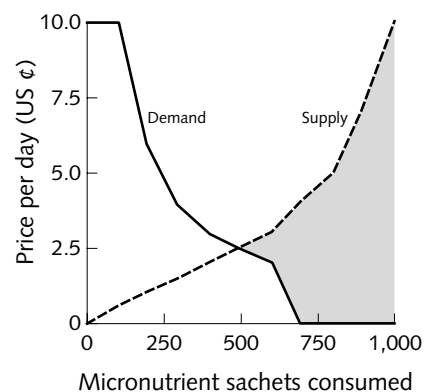FIG. 1. Model supply and demand curves showing met demand

FIG. 2. Model supply and demand curves showing unmet demand

such products are attractive to consumers in various international markets.

Where public and private organizations can then proceed to collaborate to good effect is in the transition beyond the general notion that such a product is tasty and beneficial, toward stimulating consumer demand for micronutrient products and establishing effective distribution models. Marketing activities should not simply aim to motivate consumers to want the product, but must also address ways in which it is practical for the neediest consumers to obtain it, especially the many rural poor who are so often missed by campaigns designed in urban centers. For example, partners can undertake innovative social marketing campaigns with NGOs to expound on the benefits of micronutrient supplements for mothers and children, not only through media campaigns for urban consumers but also through rolling, face-to-face rural outreach pro-grams featuring community theater, music, and non-didactic adult education. At the same time, it is vital at the outset to consider subsidizing the availability of micronutrient products at crucial contact points such as maternal and child health clinics, schools, kindergartens, refugee camps, or hospitals. Such educational and distributional efforts would raise awareness of micronutrient health and supplementation, stimulate a demand for such products on the open market, and also reach those consumers who can most benefit from and least afford to purchase micronutrient products.

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Communicating the benefits of micronutrient fortification

Marcia Griffiths

Abstract

Food fortification offers an affordable, convenient, and effective mechanism to improve the nutrition status of large segments of a population. However, the success of fortification has been less than public-health professionals and private-sector companies alike have hoped for, though often for different reasons. As new opportunities are available, success will be dictated by the ability of public health professionals to learn from private food companies' marketing efforts and, in turn, for the food companies to learn from the public health sector about how to reach groups who need fortified products the most. Simply having fortified products on the market does not promise that consumers will use the products or that businesses will continue to promote them. Carefully crafted and strategically implemented behavior-change communication can inform and motivate consumers to purchase and use the products appropriately, and, in turn, can motivate food companies, program managers, and policy makers to participate in the marketing of these products. Public health and development professionals can learn from the success of private-sector companies in creating demand for products. Good consumer research and testing can guide effective development and marketing of fortified products, as they do for all products and services. Private-sector companies that know how to market products need assistance to focus on the poorest segments of a population to pursue cost-effective strategies to get the product to those in need, in addition to those with purchasing power for the new product. Audience-specific marketing strategies can ensure that the same fortified product reaches every person who would benefit from it.

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Mention of names of firms and commercial products does not imply endorsement by the United Nations University.

Key words: Communication, food fortification, marketing, micronutrients, poverty reduction, public health

Introduction

The global climate is ready, again, for action to be taken to mitigate the urgent problem of micronutrient malnutrition. The interest and infusion of funding from the Bill & Melinda Gates Foundation and from others for the Global Alliance for Improving Nutrition (GAIN)* has helped. Even beyond this organization, groups have set goals related to reducing micronutrient malnutrition and are taking action or pledging more action. As these new programs develop and as past efforts are evaluated, there is a strong plea for improved communication and advocacy for nearly all micronutrient actions [1]. However, too frequently it is not echoed in relation to food fortification. With fortification, there is still a contingent that asks, "Is communication really needed if the fortified product is on the market?"

The resounding answer is "yes." Carefully crafted and strategically implemented communication strategies are required to ensure success in the marketplace and in public health arenas. Expertise is needed from two distinct groups: marketing professionals who work with private-sector food companies and public health or development professionals.

Scope of needed communication

In general, communication needs range from advocacy to keep fortification on the agenda of policymakers, program designers, and the food industry, to consumer education so that consumers understand the benefits of fortification. Communication can inform individuals

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* GAIN, c/o World Health Organization, Avenue Appia 20, 1211 Geneva 27, Switzerland, *http://www.gainhealth.org*

and motivate health-promoting behaviors, whether the behaviors are funding a fortification program, developing a fortified food, or purchasing a fortified food and preparing that food properly [2]. An important rule for all program developers is to never assume that the rationale for taking action that may be so clear to health experts will also be compelling to others. Each group, from policy makers to consumers, has reasons for what it does based on its own perceptions and needs. As programs try to reach each group, particularly the poor, program planners need to understand these perceptions and needs.

Key communicators of improved-health messages

There are two important but different points to make about communicating the benefits of micronutrient fortification for two very different constituencies involved in fortification programs. Although both groups share the desire to see the market of fortified products expand, each has different perspectives about what is important in the process of developing the fortified product and in bringing it to consumers. True success will come by blending the different points of view and expertise to achieve high coverage of all market segments with a product that endures. The two groups who are key in the communication process are (1) the public health or development professionals who primarily work through public institutions, and (2) the marketing and product development professionals who primarily work through private consumer-goods companies.

Public health and development professionals need help with demand creation

The first constituency, public health and development professionals, have dedicated their careers to public health research and getting programs underway to benefit the world's disadvantaged residents. They know well the nutrition angle of what will help save lives and help people to lead more productive lives. Often, they work in difficult environments, and yet have gone on to deliver the products and programs that make a difference. They have focused on the poor, usually working with developing country governments, with very little money, and sometimes with colleagues who are quite disinterested in the final outcomes.

For this group, food fortification offers an affordable, effective way to help large populations improve their nutrition situations on a daily basis. They are aware that although there have been some successes in developing and distributing fortified products to those in need, progress has been slower than desired and the gap is great between the need for and the actual availability of products for the world's disadvantaged. Some of the reasons for this disparity are the conditions under which much of this work is done, including low political priority and low budgets. While these obstacles may be difficult to overcome, one contributor to slow progress that can be changed is the way in which a fortified product and its benefits are marketed (a packaged product and the daily practice(s) related to the use of the product [3]).

Consumer demand is needed for product acceptance

Private-sector companies, such as The Procter & Gamble Co. (P&G), are full of marketing gurus and offer many lessons. The key lesson is this—*demand for a product breeds success*. P&G knows well that the best product in the world will fail without consumer demand and, unfortunately, public health and development professionals know the reverse—less beneficial products (those with poor nutrition value) can succeed because of high consumer demand. Marketers and public health professionals must work together to create and harness demand for the beneficial product.

Creating demand through innovative communication

Success in communicating the benefits of micronutrient fortification will come from capturing and learning from the lessons of demand creation or of selling. The lesson of demand creation was illustrated by P&G in 1879, when the company entered a crowded soap market with "White Soap" and linked it to the value of purity, which is very important to consumers [4]. However, the search was on for a more creative name. Ivory®, rather than White Soap, was chosen. It was distinctive and let consumers draw their own conclusions about the pure properties of the soap.

Then, as legend has it, a worker in James Gamble's soap factory left the mixing machine on too long and created soap that was so full of air that it floated. After this particular batch of Ivory was shipped out, orders began to come in for "the floating soap." P&G listened to consumers' requests and provided the product to meet them; to this day, P&G whips part of each batch and markets Ivory using the phrase "it floats." P&G's selling strategy for Ivory, to distinguish it from other similar soaps, has always been to promote those two qualities important to consumers who purchase soap—purity and the soap's ability to float. There has been no need for discussion of its ability to improve personal hygiene.

The historical successes of marketing P&G products comes from listening to consumer needs and desires: Ivory flakes, in 1919, was one of the first flaked soaps for washing clothes; Chipso, a chipped soap that dissolved better became one of the most popular in the 1920s; and in 1933 Dreft was the first synthetic detergent [5]. All were developed because P&G determined

what consumers wanted, created it, and then carefully crafted the product's appeal. They even delivered the message strategically, through a popular radio format—the soap opera.

Consumer response to changes in common products

Now consumer demand must be brought to the delivery of micronutrients. How can the benefits of fortified products be captured in terms of what consumers want? The obvious method of marketing benefits is to tell consumers about the micronutrient that has been added, the direct health benefit(s) they will receive, and any potential change the processing has meant for the product. But health benefits are not always welcome and effective in marketing.

For example, in Pakistan, use of iodized salt was promoted as a way of enhancing children's ability to gain a good education rather than a way of avoiding illness [2]; and in Bolivia, vitamin A sugar was promoted as sweet because consumers believed it would change the taste of their food or beverage [6].

Examples of successful communication campaigns

Public health and development professionals have to plan for good consumer research and product testing [7]. They must understand the properties that people want in their food, what consumers think about the addition of micronutrients, and what consumers perceive as the advantages or disadvantages of processing. For example, the process of iodizing salt results in the salt being cleaner and drier than other salt. Many people consider this a benefit and this property can be promoted. Likewise, if consumers want to be able to purchase salt in small quantities (i.e., units that cost 2 cents or measure 145 g) as they can from a vendor in the local market, then the "new" salt must be able to be sold that way. Following are summaries of some of the ways different fortified products are being promoted around the world:

Iodized salt
» Prevents loss of 10 to 15 points of IQ (Bolivia).
» "When it rains, its pours"® (advertising the dryness) (Morton® Salt, USA).

Vitamin A-fortified sugar
» For a healthy body and good eyesight (National Food and Nutrition Commission, Zambia Sugar, Zambia).
» It saves lives, it's inexpensive, and it improves health (El Salvador).
» Your family can conveniently get their vitamin A in a product they eat everyday (National Health Secretariat, Bolivia).

Fortified infant cereals
» Strengthens your baby's health and immune system (Gerber, USA).
» Enhances neurologic development and muscle strength (Gerber, USA).

Logos can create product identification

Finally, a lesson can be learned from the private sector. If the fortified product is to be sold by numerous commercial companies, or if numerous products will be fortified, it is important to identify them with a logo, such as the "Fortified with Vitamin A" symbol in Zambia or the "Vitamina A" symbol in Bolivia (see figures 1 and 2). A logo gives consumers something to look for and allows regulators to know which products carry the claim of fortification.

Private-sector companies need help reaching the poor

The second constituency that is key to making fortified food products a success is private-sector companies. These companies already know how to sell products to consumers. The questions for them are as follows: Who are the consumers to be targeted? Is the product geared to reach the poor or the people who are most in need of fortified products? Is the marketing tailored for each unique market segment?

It is true that usually a product cannot be geared for the need-based market alone—a mistake public health

FIG. 1. Vitamin A logo on Whitespoon Sugar made by Zambia Sugar, Plc.

FIG. 2. Vitamina A logo on sugar signs from Bolivia

professionals often make. But if companies are sincere in their efforts to affect public health, they need to be willing to help a product reach the segment of the market most in need—those who might not be able to afford the additional costs or perhaps can purchase only the least "processed" form, such as a product that is sold by small marketplace vendors with little or no packaging. It is one thing to provide a branded fortified product to compete with other soft drinks for example, but what about the people who do not buy soft drinks? Can a product be delivered to the poor while we market to more affluent consumers? Perhaps a minor modification in product development or packaging would allow for a product that would also be appealing and affordable to the poor.

Working together to communicate to all market segments

As a partnership forms, the public and private constituencies involved must negotiate both health-based and profit-driven matters. This can be done as the marketing strategy is constructed. It must include plans to reach not only the population that has the means to make a product financially successful by purchasing it, but also to reach the segments of the population with limited or no purchasing ability, who desperately need the benefits of the product or an alternative.

Example scenario

Following is a fictionalized case based on a true situation to illustrate the importance of each constituency reaching out to make fortification successful. The country will be called "Healthlandia." Its problem is vitamin A deficiency. Nationally, vitamin A deficiency is a borderline public health problem, but there are pockets of the country (areas with poor, indigenous population groups) where this deficiency is a serious public health problem.

The solution comes when a partnership is forged among a private-sector company that agrees to fortify sugar, the government that agrees to develop a law to make sugar fortification mandatory, and two international donors that agree to provide financial assistance to the government and the company particularly for marketing and monitoring. Conflicts arise when the government and donors want the fortified sugar to improve the vitamin A deficiency situation in poor indigenous areas, while the company wants the fortified sugar and its promotion to boost its penetration of the largest urban sugar market in the country and ensure that consumers there will buy the fortified product.

Separate marketing strategies

Conflict could have been resolved by developing two marketing strategies to address these different goals. For example, packaging needed to be different. In poor areas, 1-kg packages were not going to sell because people typically bought smaller amounts requiring less cash outlay, whereas city consumers were attracted to and *wanted* 1-kg bags to ensure they were purchasing a full measure of sugar. In addition, the benefits needed to be tailored. All consumers saw the added vitamin A as beneficial, but for the city consumers, the attraction was that it was "cleaner" than unfortified sugar because of the processing. The poorer consumers were more concerned with the taste of the sugar and "saving" it for use only on special occasions because it was so pure.

Instead of tailoring marketing materials to each of the two groups, the visuals and materials developed were aimed primarily at the urban consumers. The advertising showed people in tropical clothes leaning out of windows with open shutters along with the slogan "Come to the sweeter side of health." These visuals and this message were not effective or understood by the rural people who did not have windows with shutters in their homes and seldom even opened their windows because of the strength of the wind that blows in their region.

Success and failure of a single strategy

In the end, the marketing strategy was successful in the metropolitan area but failed in the indigenous area, despite public-sector market research. Subsequently, the government and donors believed that fortified sugar could not succeed in addressing the public health problem and lost interest in supporting the initiative. Finally, the company lost interest when the law was not enacted to support the product.

Lesson learned

The lesson here is that the poor cannot be forgotten. The bottom line is not just sales but also the improvement of the public health problem. Food companies and their marketing arms need to call on health professionals to help them understand a country's poor residents (their aspirations, perceptions, and needs) and to mobilize to assist their traditional product-delivery channels to get the product to hard-to-reach areas with the proper message.

Marketing, known and implemented so effectively by those in the private companies, can work to reach the "downscale" consumers, even those who fall below standard socioeconomic segmentation scales; but this requires reaching out, building partnerships, and accepting higher risk in many cases.

Conclusion

Developing effective communication strategies requires gathering wisdom from the two constituencies of private-sector food companies and public health or development professionals. Success will come from working together to create the demand for fortified products by tailoring products and communicating the benefits of the fortified product to each particular audience. This partnership will help achieve improvement in public health, so that micronutrient deficiencies do not continue to debilitate the billions of people affected today.

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Role of public-private partnership in micronutrient food fortification

M. G. Venkatesh Mannar and Marc van Ameringen

Abstract

Iron, iodine, and vitamin A deficiencies prevent 30% of the world's population from reaching full physical and mental potential. Fortification of commonly eaten foods with micronutrients offers a cost-effective solution that can reach large populations. Effective and sustainable fortification will be possible only if the public sector (which has the mandate and responsibility to improve the health of the population), the private sector (which has experience and expertise in food production and marketing), and the social sector (which has grass-roots contact with the consumer) collaborate to develop, produce, and promote micronutrient-fortified foods. Food fortification efforts must be integrated within the context of a country's public health and nutrition situation as part of an overall micronutrient strategy that utilizes other interventions as well. Identifying a set of priority actions and initiating a continuous dialogue between the various sectors to catalyze the implementation of schemes that will permanently eliminate micronutrient malnutrition are urgently needed. The partners of such a national alliance must collaborate closely on specific issues relating to the production, promotion, distribution, and consumption of fortified foods. Such collaboration could benefit all sectors: National governments could reap national health, economic, and political benefits; food companies could gain a competitive advantage in an expanding consumer marketplace; the scientific, development, and donor communities could make an impact by achieving global goals for eliminating micronutrient malnutrition; and by demanding fortified foods, consumers empower themselves to achieve their full social and economic potential.

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Key words: Food fortification, micronutrient malnutrition; public-private collaboration

Introduction

Iron, iodine, and vitamin A deficiencies prevent 30% of the developing world's residents from reaching their full physical and mental potential [1]. Fortification of commonly eaten foods with micronutrients offers a cost-effective solution that can reach large populations. The benefits accrue not only from reducing the burden of morbidity and mortality but also from improved school performance, parenting, and productivity. Food fortification should be part of an overall national micronutrient strategy that includes dietary promotion, supplementation, and public health measures. The expanded coverage through fortification enables those who cannot be reached through centrally processed foods to be better targeted using alternative interventions. Effective and sustainable fortification will be possible only if the public sector, private sector, and social sector collaborate to develop, produce, and promote micronutrient-fortified foods. Our focus here will be on the partnership needed between the public and private sectors.

Target partners

There are several target partners in the public and private sectors that could address micronutrient malnutrition, including the following:

» *The scientific community,* which has identified the problems of micronutrient malnutrition and conducted efficacy or clinical trials to demonstrate the benefits of fortification. Over the past decade, considerable expertise has been gained in the translation of scientific knowledge into effective programs that are supported by advocacy and social communication, legislation and enforcement, monitoring and evaluation, and training.

» *National governments*, which must provide administrative support and prescribe the framework within which solutions can be implemented and regulated.

» *The food industry*, which has technology, the capacity to mobilize resources, and the marketing capability to translate these needs into economically viable products that will be affordable and nutritious.

» *Consumers*, who need to be educated on the benefits and low cost of food fortification, thereby creating a demand to which industry would have to respond.

» *International and bilateral aid agencies*, which will provide the link and coordination between the different sectors and make them self-supporting and sustainable.

The food industry is playing an increasingly critical and complex role throughout the world. In developed countries, changes in living and marketplace patterns have stimulated changes in food industry practices, resulting in a diversity of food-processing technologies and an ever-changing array of foods on market shelves. Food fortification has played a major role in the health of these populations over the last 40 years. Recent concerns about health and the environment have resulted in significant attention to foods and food additives by regulators and legislators, the media, and educators and consumers—all the powerful groups that influence marketplace dynamics. The need for cooperation among the food industry, the scientific community, and regulators and legislators at all levels in these countries has been identified.

In developing countries, too, fortification is increasingly recognized as a sustainable long-term measure to improve the micronutrient status of large populations. Here, too, simple nutrition and technologic solutions to problems of micronutrient deficiencies exist but are often complicated by economic, social, and political factors. Intervention strategies must take into account these factors. This is the challenge as well as the opportunity for the food industry—both multi-national and domestic, small- and large-scale. In this endeavor, the food industry can draw upon active support from the other sectors. What is urgently needed is to identify a set of priority actions and initiate a continuous dialogue between the various sectors to move quickly toward the implementation of schemes that will permanently eliminate micronutrient malnutrition.

Specifically, a multi-sector partnership must be formed among industry, national governments, international agencies, expert groups, and other players to work closely on specific issues relating to technology development, food processing and marketing, free-market approaches with minimum price-support mechanisms, standards, quality assurance, product certification, social communications and demand creation, monitoring, and evaluation. Guidelines on these issues should then gain acceptance and be implemented at the national level. A multi-sector group within each country should define a feasible, affordable fortification strategy designed for the target population, identify opportunities for the involvement of the food industry, and assist in promotional and educational efforts to reach the target population.

There is a growing international dialogue in the field of micronutrient malnutrition to develop this new coalition between governments, private food companies, international agencies, and other stakeholders to discuss collaborative approaches to eliminate micronutrient malnutrition. This effort is a new kind of partnership—a partnership at different levels. At the global level, it links international agencies and groups (each with its own plans to pursue) to ensure that key issues and needs are addressed. At the national level—where the war really needs to be won—we need to link public and private sectors, profit and non-profit sectors. At the regional level there needs to be agreement on issues of inter-country food movement, standards, and regulation.

Such collaboration could benefit all sectors: National governments could reap national health, economic, and political benefits; food companies could gain a competitive advantage in an expanding consumer marketplace; the scientific, development, and donor communities could achieve impact and recognition for achieving global goals for eliminating micronutrient malnutrition; and by demanding fortified foods, consumers empower themselves to achieve their full social and economic potential.

Food fortification efforts need to be integrated within the context of a country's public health and nutrition situation and as part of an overall micronutrient strategy that utilizes other interventions as well. The basic challenge is to bridge the communications gap between the public and private sectors in understanding their needs and respective roles and responsibilities. While constraints and shortcomings do exist, there is no need to delay immediate action.

Key issues for national action

There is a critical need to initiate national dialogues to form links at the national level among government, industry, scientists, non-government organizations (NGOs), and international agencies. Key issues that such dialogues would cover include [2] the following:

Opening channels of communication

All partners need to be informed of the problem of micronutrient malnutrition and its impact. There should be mechanisms by which they communicate

with each other on a regular basis to discuss ways in which public and private resources might be brought to bear to address the problem.

Creating public awareness

Consumers should be made aware that micronutrient malnutrition diminishes the quality of their lives and that micronutrient-rich foods can play a role in a more prosperous future. How this promotion will be handled collaboratively by the public and private sectors will be one of the first issues to address.

Developing consumer demand

Informed consumers choosing to purchase fortified products over nonfortified ones will determine the success of food fortification both as a public health strategy and as a private investment. Developing consumer demand entails not simply targeting populations and promoting fortified products, but also developing the right product, price, and packaging.

Defining coverage and market segments

While the public health community seeks high coverage of large populations, the private sector targets the market to identify niches of opportunity. In several countries, large segments of the population cannot afford or do not have access to centrally processed foods. How large must a market segment be before it can be recognized as contributing to a public health goal—and therefore eligible for public recognition or support? Each national dialogue will determine its own approach to this issue.

Identifying food vehicles

Food vehicles should be selected through a process of market research that demonstrates that they are consumed by a vast majority of the population, are affordable to those most in need, and respect both political sensitivities and consumer preferences. Several food products can play complementary roles in a national fortification strategy.

Marketing campaigns

With broad agreement that public awareness and consumer demand are high priorities, collaborative public-private marketing campaigns are important issues for national dialogue. While public agencies have the credibility to market health benefits of fortification, private companies can effectively promote consumer benefits of specific products.

Keeping products affordable

Consumer prices and producer costs must be balanced, so as not to discourage demand or supply. With strong communication between public and private sectors, purchasing, processing, marketing, and distribution activities can be coordinated across market segments to keep cost increases to a minimum.

Assuring quality

Complementary public-private roles need to be defined in developing legislation and regulations, providing resources for laboratories and technical personnel, and establishing quality assurance and monitoring methodologies at the producer and retail levels.

Participation partners

A concerted effort to eliminate micronutrient malnutrition involves the active participation of several sectors. Most important are ministries of government, the food industry, and international agencies. While recognizing that national circumstances vary, a sequence of steps is necessary to initiate, develop, and sustain a national public-private dialogue:
» Public sector performs initial educational efforts
» Private sector takes the lead in market research
» Public and private sectors collaborate in developing themes and messages
» Public and private sectors partner in dissemination campaign
» Private sector tracks and fine-tunes the campaign
» Public and private sectors collaborate to revise messages
» Public sector evaluates national impact

Roles and responsibilities

Public sector

Governments need to develop political contact at the highest level and set policy and a program framework within which food fortification can be promoted. Government's primary role within this program is in education and awareness campaigns and the necessary integration. In certain cases, fiscal incentives (tax/tariff exemptions) and physical incentives (preferred access to public infrastructure) may be necessary to catalyze the process. Government could also ensure quality by providing a seal of approval to fortified foods that meet specified standards.

Private sector

The food and pharmaceutical industry could work with governments to assess mutual needs. By being part of the process from the start, industry can ensure its needs and concerns are considered. Industry has the primary responsibility of creating products and technology and developing marketing and distribution mechanisms. Industry could create "best practices" codes for production and marketing of fortified products, so that all companies can compete with regard to quality and excellence.

Conclusion

Food fortification offers a unique opportunity for the food industry to simultaneously expand its market and profitability while playing a key role in improving the physical, social, and economic well-being of a popu-lation. The food industry is capable of having a profoundly positive effect for a relatively small cost. In all countries, food fortification should be part of national priority and policy and its promotion and monitoring should be included in the government's budget. It also needs to be supported by the food industry and promoted as normal good manufacturing practice by all food processing companies. The potential benefit to the people is enormous, the costs are small, and the risks are negligible. The public and private sectors need to work together to capitalize on this opportunity to ensure that the next generation of children grows and develops to its full mental and physical potential as students, workers, and citizens.

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Public-private sector alliances for food fortification: Time for optimism*

Rolf Carriere

Introduction

The Global Alliance for Improved Nutrition (GAIN) was launched at the United Nations General Assembly Special Session on Children in May 2002 as a global and regional alliance of public, private and civic groups committed to eliminating micronutrient deficiencies. The Bill & Melinda Gates Foundation provided GAIN with its principal funding, which has been complemented by grants from international and bilateral agencies.

GAIN's vision is of a world in which malnutrition is no longer a human and social development constraint. In May 2002, the UN General Assembly Special Session on Children re-emphasized the micronutrient goals of the early 1990s: Achieving the sustainable elimination of vitamin A deficiency by 2010, reducing anaemia prevalence, including iron deficiency by one third by 2010, and virtually eliminating iodine deficiency disorders by 2005; accelerating progress towards reduction of other micronutrient deficiencies through dietary diversification, food fortification and supplementation.

The question to be asked, however, is why in 2003 are the goals for eliminating malnutrition so similar to those written at the International Conference for Nutrition (ICN) and the World Summit for Children back in the 1990s? Why does this level of malnutrition—or malnutrition at all—still persist? I'd like to review some

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Mention of the names of firms or commercial products does not imply endorsement by the United Nations University.

obstacles, which the global nutrition community must surmount, in order to make further progress. But, the take away message is that the trend is going up and success can breed success if optimism can be the dominant paradigm.

Progress and failures during the past 40 years

The past 40 years have shown unprecedented, historic progress in the field of public health, including nutrition (See table 1).

In 2000, 3.5 million fewer children died than in 1990. And, life expectancy is up dramatically. This has never happened in any era before in history. Thus, we can be successful and there is reason for hope and optimism to continue succeeding. It is important to keep in mind that even though progress has been made, there have been failures too (table 2).

Millions of people are suffering from poverty, illiteracy, infections, and early deaths.

Official development assistance funding is down; and over 36 million people are infected with HIV/AIDS. The World Bank has projected a worsening of absolute

TABLE 1. Unprecedented Social Progress from 1960 to 2001

Measure	Change from:
Life expectancy up[a]	46 to 64 years
Death among children < 5 down[a]	197 to 82 per thousand born alive
Infant mortality down[a]	126 to 57 per thousand born alive
Fertility down[a]	5.0 to 2.7 births
Enrollment in primary education up[a]	48% to 80%
Immunization up[b]	5% to 75% completing DPT3 72% completing measles

a. UNICEF, SWC 2003, Tables 1, 3, 9 [3]
b. UNDP, HDR, p. 212 [4]

TABLE 2. Continuing shortfalls

Measure	Status in 2003
Live on less than US $2/day[a]	3 billion
Live on less than US $1/day[a]	1.3 billion (40% of children in the world)
Do not attend school[a]	125 million children
No access to clean water[b]	1.5 billion
No sanitation[b]	2.4 billion
No access to electricity[a]	2 billion
Without adequate shelter[c]	1 billion
Homeless	100 million (40 million children)

a. World Bank 2003 [5]
b. UN, World Water Report 2003: 12 [6]
c. United Nations High Commission for Human Rights [7]

poverty in the next 25 years (fig. 1).

In the next 25 years, the world population is expected to increase from 6 to 8 billion. The number of people living on less than 2 dollars a day will go up from 3 to 4 billion, and the number of absolute poor will likewise increase from 1.3 to 1.8 billion. This trend will happen if we are unable to achieve the Millennium Development Goals. The report of the UN Secretary General suggests that we are *not* on the critical path to achieve the millennium goals. What will this mean for malnutrition?

Global burden of malnutrition: We have talked a lot about the global burden of malnutrition. It has been estimated that at least one third of poor countries' disease burden is due to malnutrition (Mason et al. [8]). Based on this, the global economic loss due to malnutrition could be projected at 80 billion dollars each year. These costs are based on calculations of the economic value of a population's intelligence (educability), productivity, health care costs, and the lives of millions of children and women. Yet, for about 5 billion dollars a year, the world could prevent this huge economic hemorrhage and human suffering. To address these problems, there have been many global resolutions and calls to action over the last three decades. Sometimes, they are too many to remember. Even though progress has been made, it remained painfully slow.

At present, international nutrition investments in low-income countries cover a fraction of what is needed compared to a need for about 5 billion dollars. The World Bank, whose contribution is larger than all others combined in the field of nutrition, has spent 2 billion dollars in the last 25 years. This is far below the scale where we can find sustainable and impacting solutions. Currently, the World Bank and UNICEF spend about 150 million and 50 million dollars a year in the field of nutrition, respectively. So there is
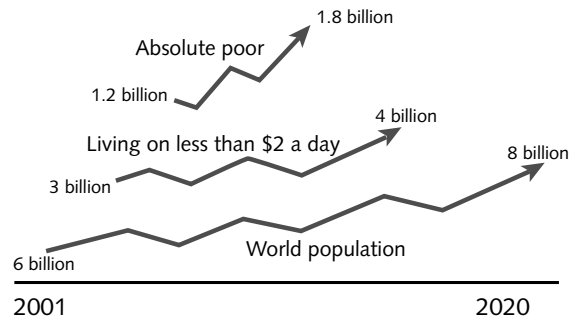

FIG. 1. World Bank Projections. Source: World Bank 2003 [5]

only one conclusion to make out of this. If we want more impact, we simply require more input. It is not a big mystery on how to achieve a dramatic impact in reducing malnutrition. Dr. John Mason recently said, (an) "average improvement rate of 0.5 percentage points per year would still only lead to zero prevalence for many countries in a century or so. There is evidence that it can be increased by interventions to around 1.5 to 2.0 percentage points/year, which brings a much more acceptable timing to solving the problem" (Mason [9]). But, why must we be satisfied with this improved, but still slow rate of decline, and another hundred years more of suffering from malnutrition when we know how to prevent the problem?

We do have the technology and we know the solutions. If we decided to do it, we could end malnutrition in a decade or two. So unless dramatic increases in resource transfers take place soon, the prospects for the human condition look dismal.

Nutrition as an investment: Nutrition is often still seen as consumption not investment, even though certain nutrition interventions are clearly excellent investments. Deficiencies such as iron, iodine, vitamin A, rob many countries of about 5% of their GDP through death and disability. Yet, micronutrient malnutrition could be effectively addressed for as little as 0.3% of the GDP (World Bank [10]). So, why does malnutrition persist? Investment in nutrition is good economics and good ethics. Then, why is it not good politics? I think there are four main reasons. These include inadequate vision, inadequate leadership, inadequate resources and a lack of psychological focus. This last reason is perhaps the most important of all—in that it keeps us unaware, unconscious or without the conscience to move forward—but this is seldom discussed.

Let me say a few words about what I mean by these:

Inadequate vision: The global development community thinks of vision as a multi-part ability that includes both the ability to see something that is there and the ability to see something that is not there—yet. Most of the world turns a blind eye towards malnutri-

tion, thinking it remains an intractable problem that we have to live with. There is no sense of urgency or moral outrage, as there are for many other global issues. Is this due to shame, denial, or powerlessness? There are others who remain convinced that malnutrition cannot be reduced before incomes increase. While malnutrition is always connected to poverty, having more money does not necessarily result in better household food distribution, and hence, nutritional status of women and children, without some education or motivating communication. The fortification of commonly consumed staples also does not require major shifts in wealth or poverty reduction before tangible benefits within a population can accrue. These inputs *can* improve maternal and child nutrition, and everyone's nutritional status, without first increasing household income. And, I would suggest that household, and community, and national income will increase once nutritional status improves. So poverty reduction is essential and should go hand-in-hand with nutrition interventions, but we cannot wait for poverty to be eliminated before starting nutrition interventions.

So, some build such a high wall around the malnutrition problem that they cannot see the opportunities for change that do exist before that wall is taken down.

Finally, there is little buy-in, beyond the small group of agencies that have always been there, for global goals to end malnutrition. There is no "citizens' action movement" for nutrition, like there are for ecology, human rights or animal protection. Most people, including many corporate CEO's, government officers and bureaucrats do not know that feasible, low-cost solutions exist. So, there are few who can see the solutions that are not there yet, but could be—and compared to the many who should be—fewer still advocating for these solutions.

Inadequate leadership: Why is it that issues that are felt to be everybody's responsibility, often wind up with no one person in charge? In some ways, nutrition suffers from over-attention, due to its multi-sectorial nature. But, because everyone involved is so careful of each other's mission, goals, comparative advantage, geographic zone of influence, i.e. "turf," nutrition has no clear champion among the international agencies, or in governments, in civil society, or in business. Those who speak for the poor, malnourished children and their mothers are typically without political clout. Also, the international community has oversold the problem and undersold the solution, which makes elimination of malnutrition appear to be a "fool's mission" for those in political power. We need to reverse this perception so that at least one highly influential leader—from each sector—takes this on as a cause that they will see through to completion.

Inadequate resources: After the Cold War ended and the peace dividend began to grow, ironically, donor and compassion fatigue set in. Development assistance in

the 1990s reached an all-time low. As shown in an analysis done by the RAND Corporation (fig. 2), governments in developing countries do not invest in nutrition for those for whom it matters most. Looking at the life-cycle of an individual, the growth of the brain happens during the first two years after birth. However, governments do not truly invest in early child development, including nutrition. As shown in figure 3, the growth velocity of children within the first two or three months is normal or perhaps even better than normal. However, between 3 to 15 months, rapid growth faltering due to malnutrition occurs. This is actually the age where the largest investment on nutrition should be made. In addition, waiting to fortify women when they are pregnant, and not when girls are growing into womanhood, is truly missing an opportunity to invest in the health of two generations at once. Finally, investments that have been made in nutrition appear to be overly "relief oriented" with little focus on economic development. Again, this is filling a
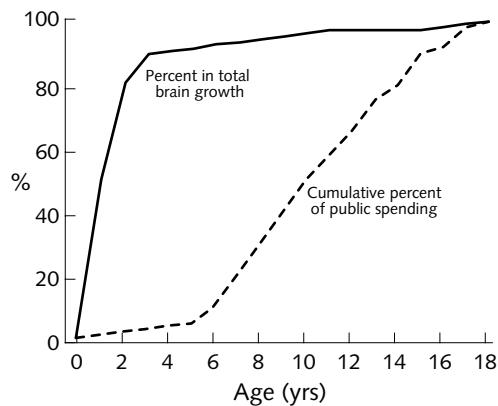

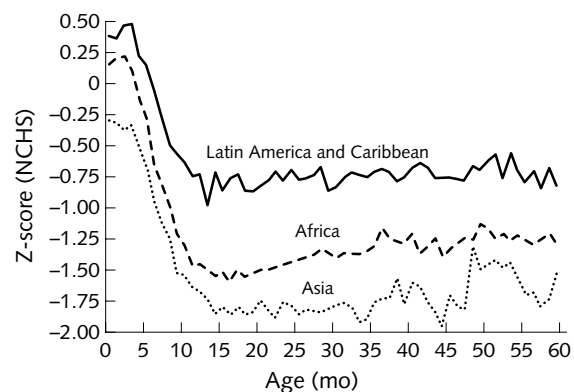FIG. 2. Brain development financing gap. Source: Karoly et al. [11]

FIG. 3. Weight for age by region. Source: Shrimpton et al. [12]

need, but it does not allow for growth.

Inadequate psychology: There is no doubt power of perception and belief allows malnutrition to persist. Many hold that malnutrition is inevitable. The reasoning goes something like this: "if we could have ended it, we surely would have done it by now. We are all decent people, we certainly don't want anybody to be malnourished, and it is inevitable, like taxes." Others may hold that malnutrition has no solution. No person on earth would tolerate such suffering if there were a solution. And finally there are those who believe that malnutrition is caused by scarcity. We don't have adequate resources to end it. These are actually unexamined assumptions, which guide and direct our thinking and our action. Unless we, as professionals in this field, rid ourselves of this perception, how can we expect others to believe that ending hunger is possible? Is ending malnutrition before the end of the decade possible? Whether you are an optimist or a pessimist, an idealist or a cynic, the mechanism of the self fulfilling prophecy is at work here. If we don't believe it is possible—it wont be. Believing is seeing. That was really what Kennedy made so clear back in 1961. He said "we will land a man on the moon and return him safely back to earth before the end of the decade." He didn't know if that was possible technically. He just had to believe in it. As a result, he was able to mobilize all the forces that were needed to actually make the man on the moon a reality. That kind of believing is also needed in our field of ending hunger and malnutrition. So malnutrition and other world problems like child labor or maternal mortality persist not only out there, but also in our minds.

And I think what we need to do is to deepen our analysis. Then we find not only objective economic, financial, political and institutional realities, but also subjective psychological forces. How do I, through my beliefs and my action, co-create the persistence of malnutrition? It is an interesting question to ponder. And I'm not saying this to send us collectively on a guilt trip. But to give ourselves another reason for deepening our involvement, by integrating the objective and the subjective, the "IQ" and the "Emotional Quotient", the consciousness and the conscience. And please, let us challenge any excuse for a closed mind.

So, why am I optimistic?

Having just started as the Executive Director for the Global Alliance for Improved Nutrition (GAIN), I see the potential for food fortification to play an important role in combating malnutrition. Now the challenge before us is how do we fortify food as fast as we can?

According to the World Bank, "No other technology offers as large an opportunity to improve lives…at such low cost and in such a short time" [10]. I think a tri-sector partnership, which consists of government (the public sector), businesses, and civil society, is needed to achieve benefits that individual sectors alone cannot accomplish. While there are many public-private sector partnerships in existence for health, this is the only one dedicated to nutrition that also includes civil society. This tri-sector partnership will make malnutrition disappear faster and at lower cost. It must be admitted that the potential role of the private sector expertise and resources has often been underestimated and even dismissed by international organizations and for too long. Also, for many years governments have tended to monopolize solutions to malnutrition. However, they are now slowly beginning to come to the conclusion that they cannot do it alone.

So I believe that partnerships offer an opportunity to bring vision, leadership and resources together in a new way, and also will or can in principle, address the psychological forces that I talked about earlier through new types of meetings, new types of encounters. Professionally facilitated meetings like "Future Search," that some of you have participated in, create a compelling vision, forge deeper alignment of many stakeholders in the whole system, and provide leadership from wherever you are in that system. But it's not going to be easy, because you need to get the public sector authorizing milieu to intersect with civil society values and business operational capacity. And it is only when you get these three sectors together that you will be able to produce the results that will bring a solution to malnutrition. There's a need to work and meet together in new ways. We must overcome mutual distrust, suspicion and antagonism without being naive. There are several good references available now on what is being learned about private-public sector partnerships for health [13–15].

The Global Alliance for Improved Nutrition (GAIN) has started its work. There is an announcement for proposals on the GAIN website to support National Fortification Alliances, many of which exist, but many need to be created. The first round of 5 grants is in progress, and our tentative target is to have 40 grants funded within 5 years, improving the nutritional status of 600 million people. This is the work of the GAIN Fund—but the Alliance will have much greater impact through the activities of its partners, including WHO, UNICEF, UNDP, CDC, USAID, CIDA and the like.

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Keynote speech: Micronutrient malnutrition

John Pepper

I'm delighted to have the opportunity to be with you tonight and grateful that you have taken the time to attend this very important colloquium. For the record, I should probably recognize at the outset that each one of you here tonight has a deeper knowledge of this subject than I do. But I would want there to be no mistake about the depth of my interest in seeing us make the kind of difference to the health—particularly of our children—that we're capable of through the effort to which we are committed.

Each of us here tonight has our own individual motivations for participating in this colloquium and in the programs that contribute to the eradication of micronutrient malnutrition. But I'm quite sure that at least these three things are shared by us all:

» The awareness of a huge gap between the nutrition that billions of people and hundreds of millions of children receive and what they need.
» The belief that we can do something about it—and soon—if we get our act together.
» The commitment to work—personally and with others—to do just this.

Certainly this is why I'm here. When I was asked if I would participate in this colloquium, it took me about two seconds to say yes. Why?

One reason is the commitment to certain principles: for one, the principle embedded in the purpose of our company, i.e., the first sentence of which commits us "Through our brands and services, to improve the lives of the world's consumers."

For another, the principle embedded in the mandate of the UN Convention on the Rights of the Child—article 24, which calls out:

» "The right of the child to the enjoyment of the highest attainable standard of health"
» The need "to combat malnutrition through the provision of adequate nutritious foods"

» And the need "to ensure that parents and children are informed, have access to education, and are supported in the use of basic knowledge of child health and nutrition"

What energizes us is also more than statements of principle. It's the knowledge conveyed by stunning if sometimes all too sterile statistics that convey a reality that can only be described as alarming:

» The knowledge that more than a hundred million children suffer from vitamin A deficiency, contributing to perhaps as many as one out of every four child deaths in areas where the problem exists.
» The knowledge that iodine deficiency is the greatest cause of preventable mental retardation in the world, with an estimated 43 million worldwide suffering from brain damage and physical impairment.
» The knowledge that anemia due to iron deficiency weakens children's learning ability and physical stamina and, not only that, it increases the risk of hemorrhage and infection during childbirth, contributing to about 20% of all maternal deaths in Africa and Asia.
» And, of course, statistics that dramatize the gap between where we should be and where we in fact are don't only apply to micronutrients. They include water, the most fundamental nutritious element of all, and the knowledge that over a billion people are currently without safe drinking water and that each year 3 to 4 million children—that's right, 3 to 4 million—a population five times the size of Cincinnati, under the age of 5 are dying from water-borne diseases.

If these statistics weren't enough to motivate us, there are our own personal epiphanies—personal experiences that have brought to life, unforgettably, for each of us the differences that we can make in the life of individuals. My epiphany came in meeting with Haile Mehansho, who has worked in the micronutrient area for more than 15 years here in The Procter & Gamble Co. Years ago now, I left his office absolutely committed to finding a way to make NutriStar® and its micronutrient technology available to all who need it.

John Pepper is Chairman of the Executive Committee, The Procter & Gamble Co., Cincinnati, Ohio, USA.

Enough on the need. It's one motivator, but there's another one and that is the *knowledge that if we get our act together we can do not just a little but a whole lot to close this gap.* Frankly, this isn't like AIDS or cancer where fundamental cures are still to be found. That's not the case with the issues we discuss here. As you well know, we have technology to deliver iodine and iron and vitamin A and zinc and other vital micronutrients and to do so at extraordinary low cost.

We also have emerging technologies (and I'm delighted that P&G is working on them), to provide safe water again at very affordable costs.

We also know many of the things that we need to do to make this technology available to those who need it. We know we need partnerships that bring together business, international agencies, NGOs, local governments, entrepreneurs, and community organizations to provide the micronutrients in products that people use, and that are affordable and that will reach them where they live.

We know we need to provide the education to establish the importance of these micronutrients and, in some cases (particularly in purifying water), instructions on how to use them.

You'll be hearing about the technologies during the course of this colloquium and I don't intend to cover them here. *I believe our three biggest challenges in actualizing the value of these technologies will be these:*

» First, finding models of operating across business, government, and nongovernmental sectors to incorporate the technologies into the right products by country.

» Second, successfully commercializing brands so that businesses like P&G can derive sufficient profit to justify continued investment in micronutrient technology and the work with governments and NGOs to make them available.

» Third, creating those partnerships tailored by country, which will be necessary to provide the education and to distribute the products to people where they live and at an affordable price.

Fortunately, we're not starting from scratch. We know micronutrient technology embedded in the right products can make a major difference in health outcomes. We've seen that with iodized salt. Thanks to UNICEF's leadership position, today 70% of all households consume iodized salt.

UNICEF's distribution of high dose vitamin A capsules at a cost of only 3 cents per dose is already saving the lives of an estimated 300,000 young children from this single supplementation program alone.

And our own clinical work in Tanzania and the Philippines is showing that NutriStar® is significantly improving children's iron blood status and that this is contributing to improvement on their nonverbal mental performance, energy, and fitness.

We also have ample experience that demonstrates that businesses *can* work together with governments and NGOs to drive important improvement in health outcomes among children and consumers generally.

P&G's own involvement in doing this goes way back, to the creation of educational programs around the use of fluoride toothpaste in the United States. Indeed, the introduction of fluoride and associated education programs in the United States has over the course of my lifetime dropped the incidence of cavities from the low teens to virtually none among young people, showing what fortification—in this case of water and dentifrice—combined with education, can do.

We've extended these relationships with government and education institutions to improve oral care to the emerging markets of the world, including Poland, China, and Russia—and research results show reductions in caries of 20–50%. In Venezuela, where we have been test marketing NutriStar,® and where 60% of youngsters have iron-deficiency anemia, we are working with UNICEF, the National Pediatric Association, and the National Institute of Space. To date, over 1.3 million children in Venezuela have consumed NutriStar.® This highlights the tremendous reach that can be achieved when public and private partners work together.

In Nicaragua, we are working with USAID, the Undersecretary of Health, and the top nutritional advisor to the country, to promote education involving NutriStar.® In total, many of the foundations required for major breakthrough are present. Technology certainly. And also conceptual understanding of what it will take in terms of organizations working together to make this technology available to those who need it.

Still, we have a long, long way to go and that is why we're here.

What will it take to achieve the success our children deserve? What any great breakthrough requires is *commitment to a stretching goal*—backing that up with a set of strategies and the right organization structure and operating plan—and impassioned strong personal leadership that gives us the right to success.

I believe the GAIN initiative, with the support it will receive from UNICEF, the Gates Foundation, and many other organizations, holds great promise as the organizing vehicle to facilitate that breakthrough. But we need to move aggressively now.

While we have an overall framework for success, we will need to tailor our programs carefully country by country. We will need to see how we can most effectively bring the micronutrients to the population, not only in NutriStar®, which I hope will be the foundation for Procter & Gamble's continued contribution with technology and know-how, but through other complementary and broadly used foods and beverages.

For example, as I speak, we are doing work in China

designed to bring iron and calcium to rice. Doing this will require the expertise and resources of multiple partners.

We will also need to work together to measure the impact of our efforts—to what extent are we improving the status of iron and other micronutrients among children? What are the specific benefits? We would all agree that it is essential that we have systems in place to monitor our collective progress in improving nutritional status and identify how to do better.

Success is there for us to grasp. It will call for us to work together toward common goals. It will require that there be a commercial payoff for business, but it will also require businesses to look beyond the bottom line, to view it as our responsibility and also in our self-interest to work with others to provide the benefits of our technologies and capabilities to a broader population than we can reach with our branded product alone.

Doing this is going to require imagination and hard work and patience as we form new relationships, iden-

tify common interests and goals, develop precise strategies and plans for each country, and share resources to achieve the goals.

Can we achieve breakthrough improvements we all seek? Clearly the opportunity is there.

Will we actually do it? Will we get beyond talk and planning and get to the strategically driven action needed to do it?

The answer to these questions will be up to us and our associates. On the one hand, I'm sure we'll make progress. The real question is whether that progress will be breakthrough or incremental. We know that breakthrough is what we need. We know it will call on our personal leadership, our imagination, our willingness to work with one another and I believe, above all, to never forget why we're doing this—to give children today what they need to grow up to be as healthy as we would want our children to be, to realize that the ability to do that is present and that there is really no excuse for us not taking the action to make it happen.