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

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 develop-
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 (ICCIDDD) 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 Malacanang 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

<table>
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<th>Box 1. Three domains of quality assurance</th>
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<tr>
<td>Essential product</td>
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<tr>
<td>raw material processing</td>
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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](image1)

![FIG. 2. Estimated number (millions) of newborns brain-protected each year, based on the percent of household availability of iodized salt, by UNICEF regions](image2)
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 smallpox 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.

References


Iron deficiency: Global prevalence and consequences

Rebecca J. Stoltzfus

Abstract

Iron deficiency is considered to be one of the 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 814,000 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

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 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

<table>
<thead>
<tr>
<th>Region</th>
<th>Population (thousands)</th>
<th>Anemia prevalence</th>
<th>Burden attributable to iron deficiency (thousands)</th>
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<tr>
<td></td>
<td></td>
<td>Women</td>
<td>Men</td>
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<tr>
<td>Africaa</td>
<td>639,593</td>
<td>41%</td>
<td>28%</td>
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<tr>
<td>Latin Americab</td>
<td>502,162</td>
<td>23%</td>
<td>11%</td>
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<tr>
<td>Eastern Mediterraneanc</td>
<td>481,635</td>
<td>44%</td>
<td>17%</td>
</tr>
<tr>
<td>Southeast Asia-IId</td>
<td>293,819</td>
<td>49%</td>
<td>32%</td>
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<tr>
<td>Southeast Asia-IIe</td>
<td>1,241,806</td>
<td>60%</td>
<td>36%</td>
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<tr>
<td>North Americaf</td>
<td>325,183</td>
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Source: Stoltzfus et al. [3]

* DALY = disability-adjusted life year
a. Excluding Egypt, Morocco, Somalia, Sudan and Tunisia.
b. Excluding Cuba
c. Including Cuba
d. Afghanistan, Djibouti, Egypt, Iraq, Morocco, Pakistan, Somalia, Sudan, Yemen
e. Bangladesh, Bhutan, Democratic People’s Republic of Korea, India, Maldives, Myanmar, Nepal (II)
f. Because anemia cutoffs are defined as the 5th percentile of a normative distribution, this represents the theoretical minimum population prevalence of anemia

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Estimate</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal mortality</td>
<td>0.80</td>
<td>0.70 – 0.91</td>
</tr>
<tr>
<td>Perinatal mortality, Africa</td>
<td>0.72</td>
<td>0.65 – 0.80</td>
</tr>
<tr>
<td>Perinatal mortality, other regions</td>
<td>0.84</td>
<td>0.78 – 0.90</td>
</tr>
</tbody>
</table>

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

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 over-dose, 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.

References

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
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
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 $\geq 3.0$ 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.

<table>
<thead>
<tr>
<th>TABLE 1. Mental scale items (12 months)</th>
<th>Infants passing (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description (item no.)</td>
<td>Anemic</td>
<td>Control</td>
</tr>
<tr>
<td>Pushes car along (99)</td>
<td>56</td>
<td>77</td>
</tr>
<tr>
<td>Turns book pages (103)</td>
<td>69</td>
<td>83</td>
</tr>
<tr>
<td>Imitates words (mama, dada) (106)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 12 months</td>
<td>13</td>
<td>47</td>
</tr>
<tr>
<td>At 15 months</td>
<td>75</td>
<td>100</td>
</tr>
<tr>
<td>Says two words with meaning (113)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 12 months</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>At 15 months</td>
<td>42</td>
<td>93</td>
</tr>
<tr>
<td>Points own toys, shoes or clothing (117)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 12 months</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>At 15 months</td>
<td>25</td>
<td>60</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 2. Motor scale items (12 months)</th>
<th>Infants passing (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description (item no.)</td>
<td>Anemic</td>
<td>Control</td>
</tr>
<tr>
<td>Walks with help (42)</td>
<td>85</td>
<td>97</td>
</tr>
<tr>
<td>Sits from standing (43)</td>
<td>67</td>
<td>97</td>
</tr>
<tr>
<td>Pat-a-cake (44)</td>
<td>82</td>
<td>97</td>
</tr>
<tr>
<td>Stands alone (45)</td>
<td>64</td>
<td>93</td>
</tr>
<tr>
<td>Walks alone (46)</td>
<td>38</td>
<td>67</td>
</tr>
<tr>
<td>Stands up from sitting (47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 12 months</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>At 15 months</td>
<td>42</td>
<td>80</td>
</tr>
<tr>
<td>Stands on left foot with help (52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 12 months</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>At 15 months</td>
<td>8</td>
<td>40</td>
</tr>
</tbody>
</table>
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 brainstem 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

![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 (\(p < 0.001\)).](image-url)
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, myelogenesis 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.
References

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

Haile Mehansho, Renee I. Mellican, Don L. Hughes, Don B. Compton, and Tomas Walter

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<sub>2</sub>, B<sub>6</sub>, and B<sub>12</sub>. 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...
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,

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

<table>
<thead>
<tr>
<th></th>
<th>Iron deficiency</th>
<th>Vitamin A deficiency</th>
<th>Iodine deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth</td>
<td>↓</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td>Mental ability</td>
<td>↓</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td>Strength</td>
<td>↓</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td>Mortality/morbidity</td>
<td>↑</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Economic development</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

**Legend:** ↓ decrease, ↑ increase, ↔ no change

**Sources:** Scrimshaw [4], Underwood [5].

**FIG. 1. Sustainable micronutrient fortification program model**
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
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

![FIG. 4. Stabilization of iron by the GrowthPlus® Technology](image-url)
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 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, B12, B6, B2, 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, B6, B2, folic acid, and B12). 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

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Fortified powder fruit drink</th>
<th>Nonfortified powder fruit drink</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall rating&lt;sup&gt;a&lt;/sup&gt;</td>
<td>44</td>
<td>45</td>
</tr>
<tr>
<td>Attribute rating&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orange flavor</td>
<td>43</td>
<td>46</td>
</tr>
<tr>
<td>Aftertaste</td>
<td>40</td>
<td>44</td>
</tr>
<tr>
<td>Color</td>
<td>44</td>
<td>48</td>
</tr>
</tbody>
</table>

<sup>a</sup> Ratings used a five-point scale (excellent, very good, good, fair, poor). Average ratings are calculated using weights as follows: 

\[
\left(\frac{(N_{ex} \times 100) + (N_{vg} \times 75) + (N_{gd} \times 50) + (N_{fr} \times 25)}{N_{total}}\right) \times 100
\]

There is no significant difference between the fortified and the non-fortified powder beverage at \( p < .05 \)
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 B12) 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 B6. 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 3. Nutrient stability in fortified powder fruit drink (in 100 g)\(^a\)

<table>
<thead>
<tr>
<th>Nutrients</th>
<th>Initial</th>
<th>12 months</th>
<th>% recovery after 12 months</th>
<th>% target value after 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron (mg)</td>
<td>54.3</td>
<td>54.8</td>
<td>100.9</td>
<td>140.9</td>
</tr>
<tr>
<td>Vitamin A (IU)</td>
<td>10963</td>
<td>10030</td>
<td>91.5</td>
<td>139.3</td>
</tr>
<tr>
<td>Iodine (µg)</td>
<td>590</td>
<td>582</td>
<td>98.6</td>
<td>143.1</td>
</tr>
<tr>
<td>Vitamin C (mg)</td>
<td>899</td>
<td>988</td>
<td>110.0</td>
<td>148.2</td>
</tr>
<tr>
<td>Zinc (mg)</td>
<td>49.6</td>
<td>49.6</td>
<td>100.0</td>
<td>118.9</td>
</tr>
<tr>
<td>Folic acid (µg)</td>
<td>797</td>
<td>873</td>
<td>109.5</td>
<td>132.1</td>
</tr>
<tr>
<td>Vitamin B12 (µg)</td>
<td>8.6</td>
<td>8.8</td>
<td>102.3</td>
<td>157.1</td>
</tr>
<tr>
<td>Vitamin B6 (mg)</td>
<td>6.5</td>
<td>7.4</td>
<td>113.9</td>
<td>132.1</td>
</tr>
<tr>
<td>Vitamin B2 (mg)</td>
<td>6.2</td>
<td>5.9</td>
<td>95.2</td>
<td>115.7</td>
</tr>
<tr>
<td>Niacin (mg)</td>
<td>33.2</td>
<td>32.0</td>
<td>96.4</td>
<td>115.1</td>
</tr>
<tr>
<td>Vitamin E (mg)</td>
<td>31.3</td>
<td>31.9</td>
<td>101.9</td>
<td>102.9</td>
</tr>
</tbody>
</table>

\(^a\) The samples were stored in a temperature-controlled room at 70°F.

### Table 4. Nutrient stability from a reconstituted fortified powder fruit drink\(^a\)

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

\(^a\) Analysis was done on fortified powder drink beverage prepared by dissolving 25 g powder fruit drink in 180 ml water.
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>
<thead>
<tr>
<th>TABLE 5. Key elements in quality assurance program</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Finished product specification and description:</strong> 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.</td>
</tr>
<tr>
<td><strong>Starting materials:</strong> 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.</td>
</tr>
<tr>
<td><strong>Production and packaging:</strong> 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.</td>
</tr>
<tr>
<td><strong>Release of finished product:</strong> 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.</td>
</tr>
<tr>
<td><strong>Documentation:</strong> 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.</td>
</tr>
<tr>
<td><strong>Training:</strong> All personnel involved in the development, manufacturing, packaging, and storing of the fortified product should be trained in quality assurance.</td>
</tr>
</tbody>
</table>

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.

References


