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Proceedings of the Colloquium "Unlocking the Potential of the World's Children through Sustainable Fortification and Public-Private Partnership" Cincinnati, Ohio, USA, 10–11 October 2002

Michael C. Latham, Haile Mehansho, and Florentino S. Solon, guest editors

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Preface

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

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

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

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

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

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

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

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

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

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

Michael Latham, Haile Mehansho,
and Florentino Solon
guest editors

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

Michael C. Latham

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

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

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

At this colloquium we addressed mainly deficiencies of iron, iodine, and vitamin A, which put more than 2 billion people at risk of deficiency-related disabilities. But as discussed in the paper, "Efficacy trials of a micronutrient dietary supplement in schoolchildren and pregnant women in Tanzania," our collaborative work in Tanzania uses a dietary supplement that contains eight other micronutrients in addition to iron, iodine, and vitamin A. And my long experience in tropical countries, particularly in East Africa, convinces me that deficiencies of some of these other micronutrients are prevalent, or occur seasonally or in times of food crises.

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

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

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

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

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

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

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

Combating hidden hunger: The role of international agencies

Nita Dalmiya, MPH, and Werner Schultink, PhD

Abstract

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

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

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

Global goals for combating hidden hunger

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

There are good reasons why such an ambitious agenda for improving nutrition was adopted. First, there was recognition that all children have a right to adequate nutrition. This was first articulated in the Universal Declaration of Human Rights adopted in 1948, and most recently expressed in the Convention on the Rights of the Child (CRC) which has been ratified by 192 countries [4]. Second, good nutrition is recognized as the foundation for survival, growth, and development of children. Well-nourished children have improved health, perform better in schools, grow into healthy adults, and have longer life expectancy. Well-nourished women face fewer risks during pregnancy and their children start life both physically and mentally healthier. Moreover, it was recognized that fetal and infant malnutrition have the most serious and long-term consequences, particularly on the development of chronic diseases in later life. Plus, there is considerable evidence that malnutrition is a contributing factor in half of all deaths in children under 5 years of age [5]. This is true not only for severe and moderate malnutrition but also for mild malnutrition. In addition, the importance of micronutrients—particularly iodine, iron, and vitamin A—to the survival, health, and cognitive development of children had gained wider recognition.

Progress toward combating hidden hunger

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

Vitamin A deficiency

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

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

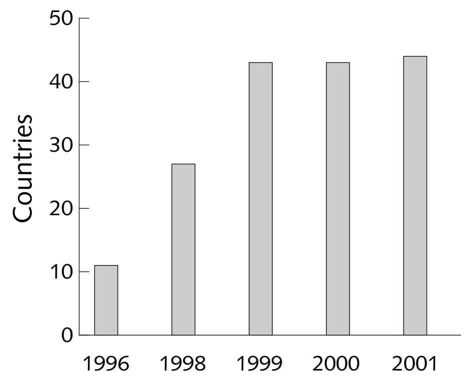

FIG. 1. "Rapid progress." Number of countries with high vitamin A supplementation coverage (one dose)

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

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

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

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

Iodine deficiency

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

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

Dramatic progress has been made during the last decade toward eliminating iodine deficiency. Household consumption of iodized salt more than tripled during the last decade. In 2001, 70% of households in the developing world were estimated to consume adequately iodized salt (fig. 3). The countries of Latin America and the Caribbean achieved the highest levels of iodized salt coverage (81%) followed closely by East Asia and the Pacific at 80%. The Middle East and North Africa stood at 70%, followed by sub-Saharan Africa at 68%. South Asia lags behind at 55% mainly due to slow implementation in India and Pakistan. In central and

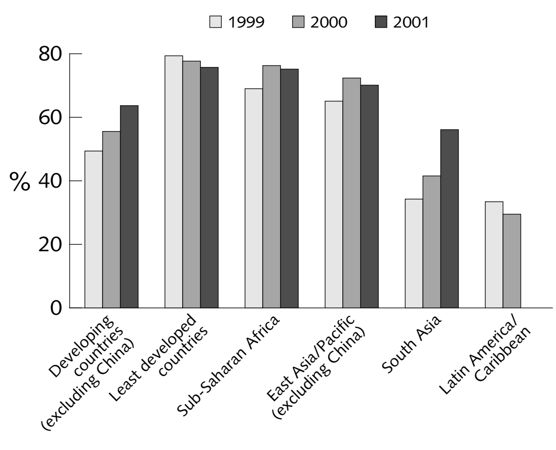

FIG. 2. Vitamin A supplementation in the developing world. Percent of children aged 6–59 months who received at least one vitamin A supplement

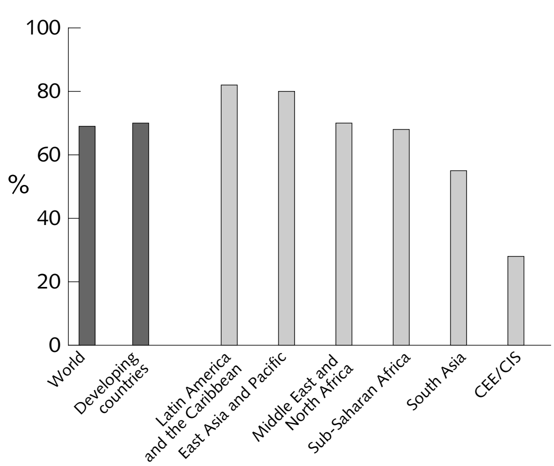

FIG. 3. Levels of iodized salt consumption (1997–2000). Percent of households consuming adequately iodized salt

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

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

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

Iron-deficiency anemia

Iron deficiency is a global nutrition problem affecting the health of billions of people worldwide, with subsequent impact on the economic performance of affected nations. The WSC goal of reduction of iron-deficiency anemia in women by one-third of the 1990s levels was closely linked to maternal health. The main intervention to reduce anemia in pregnant women was the distribution of iron-folate supplements to pregnant women through the public health system. While several governments of developing countries have expanded coverage of iron supplementation using their own resources, the bulk of support for iron-folate supplementation programs comes from external resources, such as the government of the Netherlands and the Micronutrient Initiative. Between 1993 and 1996, UNICEF supported 122 countries in distributing more than 2.7 billion iron supplements to pregnant women [14]. An additional 1 billion iron-folate tablets were distributed over the 2-year period of 1999–2000 [14]. Iron supplementation was perceived as a doable strategy because of its proven impact on anemia and because iron supplements are cheap, at a price of approximately $1.50 (US) per 1000 tablets.

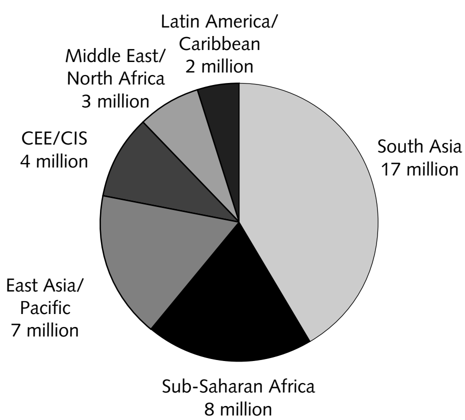

FIG. 4. Forty-one million newborns still unprotected from learning disabilities caused by iodine deficiency

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

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

Reducing anemia may only be achieved through a combination of strategies. Supplementation with iron and folate during pregnancy remains an important strategy, but acceptance-related problems must be overcome. Supplementation should include other nutrients, because anemia can be due to deficiencies of other nutrients as well, including vitamin A, zinc, and vitamin B_{12}. Multiple-micronutrient supplementation, rather than iron-folate supplementation alone, is now being investigated in pilot trials as an option to reduce anemia and improve intrauterine growth. Food fortification is another strategy that needs to be pursued more rigorously, including partnerships with the food industry. Prevention of diseases, such as malaria and helminthic infection, should also be part of an overall strategy to reduce anemia. In addition, it should be recognized that anemia is highly prevalent among young children, especially in South Asia and sub-Saharan Africa. This condition has a marked negative impact on child development. Programs to address anemia in young children must also receive greater priority and should include multiple-micronutrient supplementation.

Achievements and opportunities

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

Finally, an important achievement of this decade has been the increased awareness of the role of nutrition in early child development as well as in human development and poverty alleviation. A major opportunity to make further progress in this regard is provided by the World Fit for Children (WFC) and the Millennium Development Goals. The WFC goals focus on reducing malnutrition in children under 5 years of age by at least one-third through supportive strategies that include the sustained elimination of vitamin A and iodine deficiencies by 2005; reduction by one-third in the prevalence of anemia, including iron deficiency, by 2010; and accelerated progress toward reduction of other micronutrient deficiencies, through dietary diversification, food fortification, and supplementation.

The role of international agencies

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

Advocacy, partnership, and alliance building

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

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

The Network for the Sustained Elimination of Iodine Deficiency, which was launched at a special session of the United Nations general assembly in May 2002, is another example of an “alliance” of organizations, including salt producers’ associations, UN agencies, international non-governmental organizations, research institutions, civil society organizations, professional bodies, and private foundations that are all committed to fulfilling the World Fit for Children (WFC) goal on iodine nutrition. Among its various activities, the network through its member organizations supports the formation of "national watches" at the national level, bringing together government, international organizations, the salt industry, civil society organizations, and consumer groups in favor of sustained iodine deficiency elimination. Similar coalitions using this model are being formed to support other food fortification initiatives at the country level.

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

Technical support for implementation of national programs

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

Mobilization of the private sector

Equally important was the realization that some of the solutions to the micronutrient problem lay outside the public-health sector and that it would therefore be crucial to work with the private sector to make a positive impact on a population's micronutrient status. International agencies have stimulated public-private cooperation at the international and national level on food fortification. In country after country, international agencies such as UNICEF have worked to remind producers of their "social responsibility" to iodize salt. Several meetings of salt producers were organized to bring together salt producers on a regional basis between 1999 and 2000 in Africa (Mombasa, Accra, and Dakar), Latin America (Bogota), and in eastern and central Europe/Commonwealth of Independent States (Kiev). A mini-symposium on the benefits of iodized salt was also included at the Salt2000 Symposium held in The Hague in May 2000. Similar dialogue and efforts with private industry are ongoing in other areas of food fortification, such as with sugar producers and flour millers.

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

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

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

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

Direct fundraising and leveraging of other sources of funding

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

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

Promoting a rights-based approach

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

Support for monitoring and evaluation

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

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

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

Conclusion

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

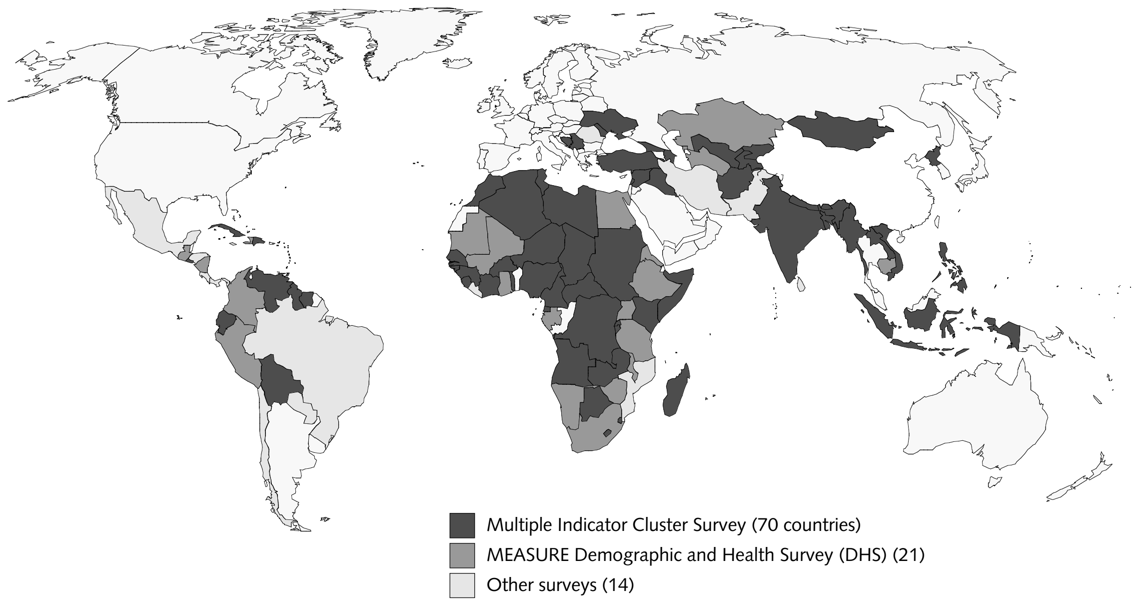

FIG. 5. End-decade household survey activity

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Vitamin A deficiency disorders in children and women

Keith P. West, Jr.

Abstract

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

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

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Introduction

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

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

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

this micronutrient deficiency in disadvantaged populations.

Prevalence and burden of vitamin A deficiency

Estimates of extent and severity of vitamin A deficiency are imperfect, as they depend on the frequency of use of valid indicators of vitamin A status across populations, and draw on diverse sources of data of varying representativeness. In chronically deficient regions, reports that are based on xerophthalmia in children [3] and night blindness in pregnant women [4] can provide highly specific data on moderate-to-severe vitamin A deficiency. Dark adaptometry provides a recently standardized, valid approach to quantify the prevalence of mild scotopic vision loss attributable to vitamin A deficiency [5] but has been insufficiently used to date for estimating burden of deficiency. Stable isotope use allows measurement of total body stores of vitamin A and validation of other indicators of status [6], while the relative dose response remains a useful research tool for indirectly assessing hepatic retinol adequacy [7]. However, assessing liver or total body stores of vitamin A by these means remains difficult, expensive, and little used in large population studies. Although new and simpler assessment tools are being developed, determination of vitamin A deficiency in most populations rests on interpreting distributions of retinol content of serum or plasma [8, 9] and, among women, also in breast milk [10]. Conjunctival impression cytology (CIC) has also found wide use in assessing population prevalence of vitamin A deficiency [5], particularly when serologic data could not be collected. These latter measures of status have been used by the World Health Organization (WHO) [11, 12], the Micronutrient Initiative (MI) [13, 14], and the International Vitamin A Consultative Group (IVACG) [15] to estimate or monitor changes in the burden of vitamin A deficiency in children and, more recently, estimate the extent of deficiency in pregnant women [15].

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

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

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

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

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

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

Source: West KP Jr. [15]

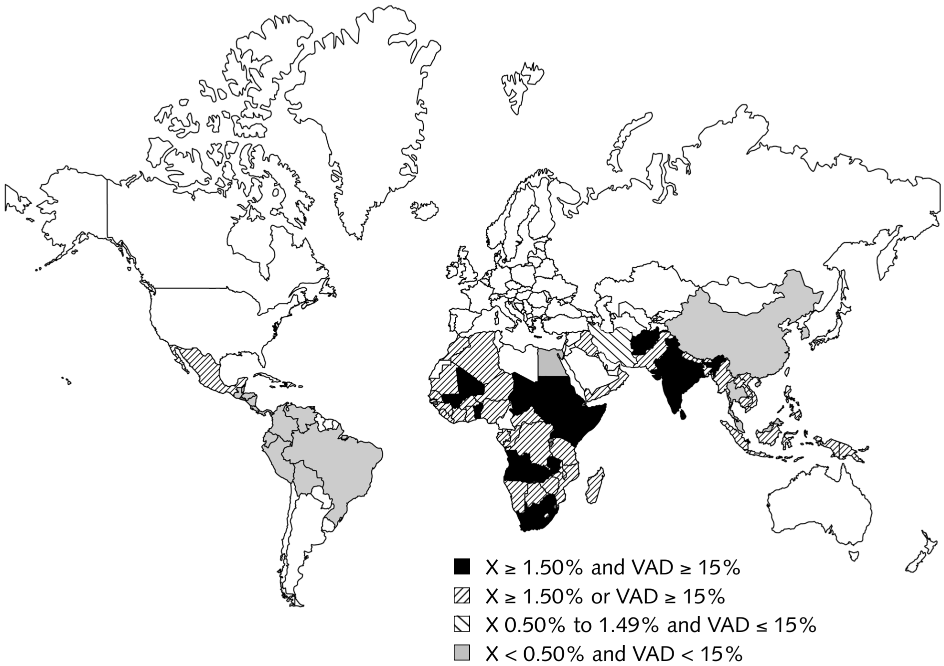

FIG. 1. Global distribution of preschool vitamin A deficiency (VAD), defined by serum retinol concentrations < 0.70 µmol/L or abnormal impression cytology and all active stages of xerophthalmia (X) at cutoffs that recognize recent IVACG recommended cutoffs. Source: West KP Jr. [15] *Reprinted with permission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

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

Chronic vitamin A deficiency appears to affect women during their reproductive years. Recently, it has been estimated that nearly 20 million pregnant women in a given year have low vitamin A status (with SROL or breast milk vitamin A concentrations < 1.05 µmol/L), of whom 7 million are deficient (concentrations < 0.70 µmol/L) and 6 million experience gestational night blindness (XN) [15] (table 2). By these estimates, nearly two-thirds of the world's night-blind women live in South and Southeast Asia, of whom 75% live in India, although this provisional global distribution may be reflecting, to a degree, more adequate population assessment of maternal XN in India than other high-risk countries at present for which conservative assumptions were applied to obtain numbers of cases.

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

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

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

Source: West KP Jr. [15]

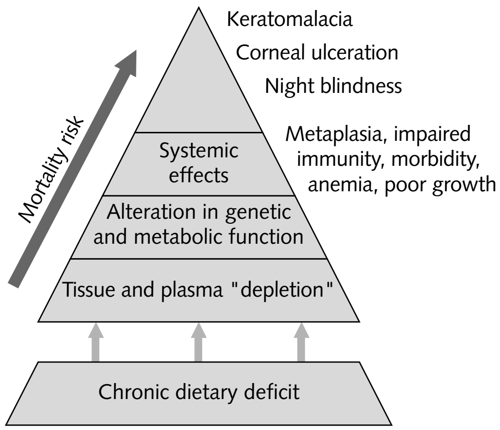

FIG. 2. Conceptualization of vitamin A deficiency disorders (VADD). Chronic dietary deficit is not a VADD, but a chronic, underlying cause that gives rise to vitamin A-deficient tissues and consequent disorders. Source: West KP Jr. [15] *Reprinted with permission from the American Society for Nutritional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

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

Vitamin A deficiency disorders (VADD)

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

VADD in preschool children

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

Xerophthalmia

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

Infectious diseases

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

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

retinol that can result in health consequence.

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

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

Poor growth

Vitamin A is essential for mammalian growth [54]. Although vitamin A is doubtless needed for child growth, isolating its effects amidst other growth-limiting insults (coexisting nutrition deficiencies or infection) has proven difficult. Children with mild xerophthalmia are often stunted [1, 37] and may exhibit some degree of wasting [37, 55]. Incident or chronic mild xerophthalmia is associated with slowed pondostatural growth, but the dominating height deficit observed in cross-sectional studies may, in part, result from more complete catch-up in weight than height during recovery from one or more xerophthalmic episodes in the preschool years [34]. The more severe the vitamin A deficiency or illness, the greater the chances that supplementation will improve either linear [35, 56, 57] or ponderal [40, 57–60] growth. Effects where present, however, may be seasonal [35, 59], age- or sex-specific [57, 58, 60, 61], and may be modulated by disease factors, such as duration of respiratory infection [62] or intestinal worm burden [61], which makes the growth response difficult to predict as a public health benefit of vitamin A deficiency control. The often-noted lack of impact of vitamin A supplementation on child growth in diverse populations [63–65] may reflect relative adequacy of pre-existing dietary vitamin A intake to support levels of growth possible in a particular setting, modulating effects by other nutrition deficiencies on growth or vitamin A utilization, persistent infection, adequacy of health care, or study design factors that could mask effects (e.g., exclusion criteria, duration of study).

Anemia

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

Child mortality

There is consistent evidence that an increased intake of vitamin A, achieved by supplementation or food fortification, can improve survival of older infants and preschool aged children. On the other hand, vitamin A supplementation below 6 months of age may or may not improve early infant survival, which is presently driving public health research.

Infants and children 6–72 months of age. Motivated by observations in the late 1970s of higher mortality risk among mildly xerophthalmic children [38], eight community trials involving more than 177,000 preschool aged children were carried out in the 1980s and 1990s in Southern Asia and Africa to examine the effects of vitamin A supplementation in reducing mortality among preschool children. Six trials observed statistically significant reductions in mortality from all causes in vitamin A–supplemented children compared with children in control groups. Interventions that have been tested include periodic high-potency vitamin A delivery (200,000 IU in infants > 12 months old, half-dose in infants 6–11 months old, every 4–6 months), which reduced death rates by 19–34% [68–71]; weekly low-dose (8,000 IU) vitamin A delivery that lowered mortality by 54% in one trial [72]; and fortification of monosodium glutamate, a flavor enhancer, that reduced mortality by 45% when consumed by preschoolers at a level that provided approximately one-third of a recommended dietary allowance (RDA) [56] (fig. 3). The findings suggest that consuming vitamin A in smaller, more frequent doses through diet or supplements could be more protective, albeit programmatically more demanding, than periodic use of high-potency vitamin A. Although two field trials failed to find a significant impact of vitamin A on survival [73, 74], published meta-analyses have suggested that the effects of these trials are compatible with an underlying reduction in preschool child mortality of 23–34% [1, 75, 76]. The findings are most relevant to underdeveloped settings where children are chronically exposed to undernutrition, where high levels of morbidity are coupled with inadequate health care and other social services, and where a resultant excess of childhood mortality exists.

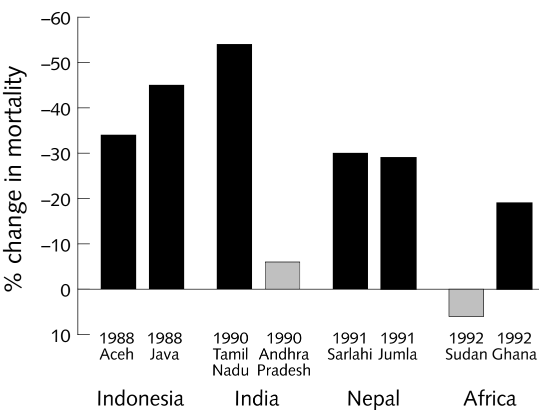

FIG. 3. Percent reductions in preschool child mortality attributed to vitamin A supplementation or fortification obtained from eight large field trials in Southern Asia and Africa between 1982 and 1992. Dark bars denote statistically significant reductions in child mortality with vitamin A. Source: Sommer A, West KP Jr. [1]. From *Vitamin A Deficiency: Health, Survival, and Vision*, by Alfred Sommer and Keith P. West, copyright 1996 by Oxford University Press, Inc. Used by permission of Oxford University Press, Inc.

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

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

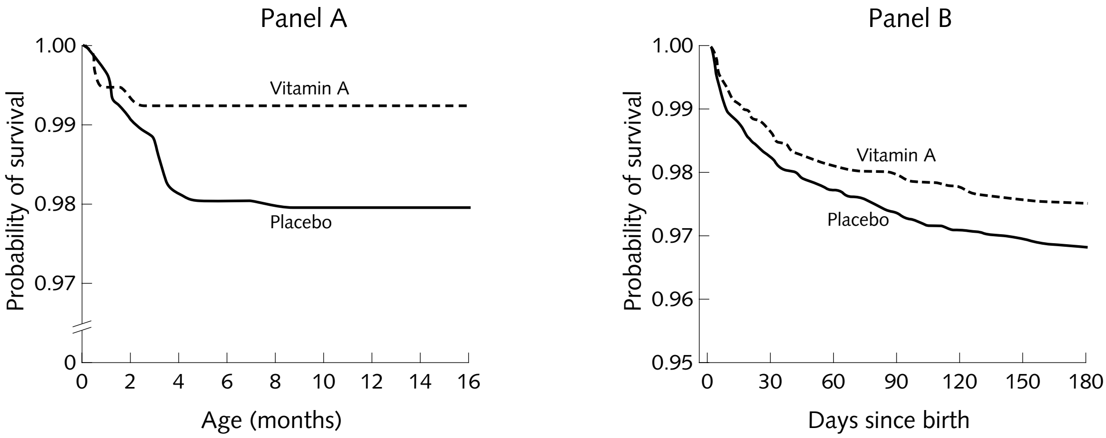

FIG. 4. Panel A: Survival curves from birth into the second year of life for Indonesian newborns randomized to receive vitamin A (50,000 IU) or placebo. Spread between lines represents a 64% reduction in mortality attributed to vitamin A receipt. Source: Humphrey JH, et al. [83]. Reprinted from the *Journal of Pediatrics*, with permission from Elsevier.

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

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

VADD in pregnant and lactating women

Evidence is emerging to reveal that maternal vitamin A deficiency is associated with significant health risks. Night blindness is a xerophthalmic symptom that can affect 5–15% of pregnant women in an undernourished population. Maternal history of night blindness also serves as an indicator of vitamin A deficiency among women of reproductive age and in the community, with a minimum cutoff set at 5% [4]. In Nepal, mothers reporting to be night blind in the third trimester were more likely to be anemic (odd ratio [OR] = 3) and report symptoms of urinary or reproductive tract infection (OR = 2.1), diarrhea or dysentery (OR = 3.4), or nausea, vomiting, and poor appetite (OR = 2.1) [94]. Cases were also more likely to have reported symptoms consistent with urinary/reproductive tract infection (OR = 1.9), upper gastrointestinal upset (OR = 2.7), and pre-eclampsia 2–3 months before their first report of night blindness [94]. These cases were at about the same mid-gestational age as mothers from another prospective series, who themselves developed night blindness later in pregnancy and who were found to have lower mid-pregnancy serum retinol, retinol-binding protein, and transthyretin concentrations than women never experiencing the condition [95]. While infection may have contributed to the hyporetinolemia [30], it is likely that chronic vitamin A deficiency preceded infection, because it has been observed that night blindness tends to recur during repeated pregnancies [96]. Studies from Nepal have also revealed a four-fold higher mortality among women who had developed night blindness during pregnancy for up to 2 years following the index pregnancy outcome, primarily associated with infectious causes [97]. Thus, maternal night blindness appears to flag mothers who are vitamin A deficient and at increased risk of poor health possibly due, in part, to underlying vitamin A deficiency and other associated causes.

Milder, non-xerophthalmic vitamin A deficiency in mothers also appears to contribute to anemia. In the plains of Nepal, 14% of all maternal anemia (Hb < 110 g/L) and 29% of moderate-to-severe anemia (Hb < 90 g/L) could be attributed to low vitamin A status (SROL < 1.05 μmol/L) [98]. Low-dose, daily supplementation of pregnant Indonesian women with vitamin A (2400 μg retinol equivalents [RE]) for 2 months raised Hb by 6 g/L over placebo recipients, versus a 10 g/L increment obtained with iron alone (60 mg/d) and a 15 g/L increment when both iron and vitamin A were given, reflecting a role for vitamin A alone and in combination with iron in preventing anemia [99]. Similar additive effects of vitamin A on hematologic indicators in pregnancy have been observed elsewhere [66, 67].

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

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

Prevention of vitamin A deficiency

Vitamin A deficiency can be controlled as a public health problem by maintaining adequate intakes of the nutrient in high-risk groups through direct supplementation, fortification, agronomic programs, marketing, and educational efforts to improve diet. The epidemiology of VADD, particularly well-described for mild xerophthalmia [1, 105], can provide a basis for targeting and program design. For example, the prevalence of mild xerophthalmia in children may increase seasonally with cases tending to cluster by province, village, and within households [106]. Taking both of these time and location factors into consideration, six monthly, high-potency vitamin A supplements (e.g., 200,000 IU for children ≥ 12 months; half this dose at 6–11 months of age) [107] should be timed to precede the peak xerophthalmia season by at least a month. High vitamin A supplementation coverage has been achieved in recent years through the conduct of well-coordinated campaigns occurring every six months. National Immunization Days (NIDS) that include polio vaccination, for example, have provided opportunities to cover preschoolers once a year [18]. Often NIDS-based vitamin A delivery has been complemented by vitamin A distribution through other child health or stand-alone campaigns during alternating six-month periods [26]. For smaller programs, knowledge that VADD clusters by a factor of ~2 within villages and a factor of 7–10 among siblings of the same household [106], who tend to consume diets similar to cases [108], suggests that health care providers should do the following: (1) treat the xerophthalmic child (or night-blind mother) [3]; (2) dose prophylactically preschool-aged siblings of the case (or young children of a night-blind mother); (3) evaluate and provide dietary advice to the family of a case; and (4) broadly implement supplementation, gardening, or counseling programs in communities from which cases originate.

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

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

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

Conclusion

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

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