

THE EFFECT OF

VITAMIN A

NUTRITURE

ON HEALTH

A REVIEW

Ritu Nalubola and Penelope Nestel

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Foreword

Vitamin A deficiency is a significant public health problem. The World Health Organization estimates that at least 250 million preschool-age children are subclinically deficient and about 3 million have clinical xerophthalmia. About 10% of all blind children are blind because of vitamin A deficiency and about 70% of them die within 1 year of becoming blind.

Over the past 15 years, research has shown that improved vitamin A nutrition would reduce all-cause mortality rates among children less than 5 years old by 23% and prevent 1.3 to 2.5 million deaths annually. Moreover, the 1993 World Bank Development Report showed vitamin A intervention to be one of the most efficient in terms of both cost and improvement in the quality of life.

Although vitamin A is important for survival, the mechanisms are not clear. It is known to enhance immune function and help fight infection, and its role in the progression or transmission of human immunodeficiency virus (HIV) infection is now coming to the forefront of science. Evidence is also growing for other beneficial roles of vitamin A in health, including during pregnancy and lactation.

This document provides a comprehensive summary of published research on vitamin A nutrition and health. The intention is to provide a state-of-the-art review of our knowledge base that will assist in planning programs as well as identifying gaps in our knowledge.

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1. INTRODUCTION

The leading causes of child morbidity and mortality in developing countries include several communicable diseases that have been associated with a lack of adequate vitamin A. This group of diseases includes diarrhea, measles, acute respiratory illness, helminth infections, malaria, tuberculosis, human immunodeficiency virus (HIV), and vaccine-preventable childhood infections. Collectively these conditions have been attributed by the World Bank (1993) to be responsible for more than 30% of disability-adjusted life years lost in the developing world.

Intervention programs to prevent vitamin A deficiency include four to six monthly administrations of high-dose vitamin A supplements to children less than 5 years of age and specific targeted approaches. However, few, if any, data exist to show that routine provision of vitamin A supplements through the regular health care delivery system is effective, which indicates that greater efforts are needed to integrate vitamin A activities into child survival programs.

The purpose of this document is not to examine the need for vitamin A interventions per se but to review the current literature on vitamin A and health in order to help provide guidelines to policy makers, program planners, and educators involved with vitamin A interventions and research to support such interventions.

Chapter 2 describes the selection procedure for the studies presented, and the next seven chapters review case-control studies, cross-sectional surveys, controlled intervention studies, and other ad hoc studies on issues related to vitamin A and health: common infections (Chapter 3), immunity (Chapter 4), HIV infection and transmission (Chapter 5), immunization (Chapter 6), toxicity and safety in pregnancy (Chapter 7), during lactation (Chapter 8), interactions with iron or zinc (Chapter 9), and β -carotene as a source of vitamin A (Chapter 10). Each chapter includes a discussion of the key findings, including methodological limitations, confounding factors, and conclusions. Chapter 11 provides an overview of the data on vitamin A and health and discusses the broader program and policy issues and their implications. Ongoing research and future research needs are also summarized in Chapter 11. Tables summarizing the studies are presented in Annex 1.

The evidence for a beneficial role of vitamin A in reducing mortality in children is conclusive and has not been included here as the subject has been thoroughly reviewed in three recent meta-analyses (Fawzi et al. 1993, Glasziou and Mackerras 1993, Beaton et al. 1992).

2. METHODS

The scientific literature on the effect of vitamin A nutriture in health was amassed from a Medline search for the years 1966 through 1998. Review articles were also used as sources of references on relevant topics. All relevant scientific studies published in English language peer-reviewed journals as well as statement or position papers of international organizations such as the World Health Organization (WHO), United Nations Children's Fund (UNICEF), or United States Agency for International Development (USAID) were included. Presentations made at scientific international or national conferences, such as the meeting of the International Vitamin A Consultative Group, the International Union of Nutritional Sciences conference, or the Annual Experimental Biology meeting were not included.¹

The findings of the different investigations have been reviewed and any broad-based limitations of the studies, and confounding factors that may explain conflicting results, are presented. This is followed by a critical evaluation of key studies. The design of every study, however, was not critically analyzed for specific strengths and weaknesses.

Research articles that report original results are tabulated in Annex 1. Other articles that present a review of scientific findings or provide a position statement of an organization are not tabulated; however, they are cited as references in the text. Thus, not all the articles cited in the text can be found in the tables in Annex 1.

¹ Abstracts on vitamin A research are listed in the "USAID inventory of current vitamin A research and program activities related to child survival in developing countries" that is available from ILSI.

3. EFFECT OF VITAMIN A ON MORBIDITY DUE TO INFECTION

Vitamin A plays an important role in the body's ability to develop an immune response to infection as is discussed in Chapter 4, which describes the role of vitamin A in immunity. Two facts to consider in reviewing the role of vitamin A in infectious morbidity are

- Infection can result in vitamin A deficiency through decreased absorption, increased utilization, and increased excretion of vitamin A and through reduced overall food intakes.
- Vitamin A deficiency can increase the risk of infection, and supplementation with vitamin A can alleviate morbidity symptoms caused by infection.

Infection As a Risk Factor for Vitamin A Deficiency: Case-Control Studies

Various infectious diseases, including diarrhea (WHO 1988a), measles (Anonymous 1987, Sauter 1982), respiratory infections (Sivakumar and Reddy 1972), and parasitic infections are risk factors for vitamin A deficiency. Sixteen case-control studies reported that vitamin A deficiency is more prevalent among children with infection than in those without (Annex Table 1). Semba et al. (1996) found that 73% of children with bacterial meningitis had subclinical (serum retinol < 0.7 µmol/L) and the residue had severe (serum retinol < 0.35 µmol/L) vitamin A deficiency. Serum retinol levels were lower in children with diarrhea than in those without diarrhea (Salazar-Lindo et al. 1993, Bloem et al. 1990a) and were negatively associated with the duration of diarrhea before hospitalization (Alvarez et al. 1995). Serum retinol was also reported to be lower in children infected with *Shigella dysenteriae* type I; this decrease was independently associated with high fever and low weight-for-age (Mitra et al. 1998b). Low serum retinol levels were also observed in children with a history of respiratory disease (Quinlan and Hayani 1996, Bloem et al. 1990a, Sivakumar and Reddy 1972).

In Thailand, severe vitamin A deficiency was observed in about one-third of children with measles (Varavithya et al. 1986). Reddy et al. (1986a) reported that low serum retinol and retinol-binding protein (RBP) levels were highly prevalent during the acute stage of measles. Coutoudis et al. (1991b) also found that serum retinol and RBP levels were significantly lower in measles patients compared with healthy control subjects. Measles was an important risk factor for severe vitamin A deficiency and blindness in malnourished African children hospitalized with measles (Inua et al. 1983, Sauter 1982).

Friis et al. (1996) observed that for every 100 eggs per g of feces increase in *Schistosoma mansoni* concentration serum retinol levels decreased by 0.03 µmol/L, which suggests that a high intensity of parasite infection induces vitamin A deficiency. Low serum retinol and RBP levels in the presence of schistosomiasis infection were also observed in Egyptian patients by Mikhail and Mansour (1982a, 1982b) and in Liberian adults and teenagers by Sturchler et al. (1983). Tanumihardjo et al. (1996) found that vitamin A deficiency was commonly observed in children infected with *Ascaris lumbricoides*. Serum retinol has also been reported to be significantly lower in children with malarial infection (Filteau et al. 1993, Tabone et al. 1992, Galan et al. 1990, Sturchler et al. 1987).

Reduced absorption, increased utilization, increased excretion, and reduced food intakes (due to anorexia associated with morbidity) are known to contribute to vitamin A deficiency in the presence of infection. Vitamin A absorption is greatly reduced in acute diarrhea (WHO 1988a, Reddy et al. 1986b), gastroenteritis (Sivakumar and Reddy 1972), measles (Anonymous 1987), respiratory infection (Sivakumar and Reddy 1972), and some parasitic infections (ascariasis: Marinho et al. 1991, Mahalanabis et al. 1979, Mahalanabis et al. 1976, Sivakumar and Reddy 1975; giardiasis: Marinho et al. 1991, Mahalanabis et al. 1979). Ahmed et al. (1993a), however, reported that infection with *Ascaris* does

not predispose children to malabsorption of vitamin A, but the small sample size may have influenced the results in this investigation. Besides reduced absorption, the utilization of vitamin A is greatly increased in parasitic infections. Urinary loss of vitamin A during pneumonia or sepsis is a recognized phenomenon (Stephensen et al. 1994). Urinary excretion of vitamin A is also strongly associated with rotavirus diarrhea and fever (Alvarez et al. 1995) and shigellosis (Mitra et al. 1998a) in children.

Vitamin A Deficiency As a Risk Factor for Infection: Case-Control and Cohort Studies

Because vitamin A deficiency impairs immunocompetence, the body may become more susceptible to infectious agents. Indeed, in case-control and cohort observations, vitamin A deficiency has been reported to be a risk factor for several infections (Annex Table 1). Shahid et al. (1988) found that vitamin A deficiency increased the risk of persistent diarrheal morbidity in children. Similarly, Sommer et al. (1983, 1984) reported that Indonesian children with mild xerophthalmia were three times more likely to report diarrhea than those with no signs of vitamin A deficiency. Fawzi et al. (1995) found a strong inverse association between dietary intakes of vitamin A and the risk of diarrhea or the risk of cough and fever in Sudanese children 6 months to 6 years old.

Sommer et al. (1983, 1984) also reported that respiratory infections were more common in Indonesian children with xerophthalmia, and the prevalence increased with the severity of xerophthalmia. Vitamin A deficiency, however, was not associated with increased prevalence of measles or chickenpox. Bloem et al. (1990a) found that vitamin A deficiency (serum retinol < 0.35 $\mu\text{mol/L}$) increased the risk of respiratory disease fourfold among children in Thailand. Vijayaraghavan et al. (1990) also observed an increased risk of respiratory infection in mildly xerophthalmic preschool children in India.

Vitamin A Supplementation and Morbidity: Controlled Intervention Studies

Many studies have looked at the association between vitamin A supplementation and morbidity. Never-

theless, a distinction needs to be made between studies that were set up primarily to evaluate the effect of vitamin A supplementation on morbidity and those that were set up to evaluate mortality. This separation is important because the latter examined the prevalence of morbidity only in cross-sectional surveys repeated every 3 to 4 months. A third category includes studies that looked at the effect of vitamin A therapy during and after an acute episode.

Diarrheal Morbidity

Vitamin A deficiency was identified as a risk factor for diarrhea in field observational studies (Shahid et al. 1988, Sommer et al. 1983). Annex Table 1 lists the controlled interventions on supplementing children with vitamin A deficiency with oral doses of vitamin A.

Several researchers have shown that vitamin A supplementation decreases the incidence and prevalence of diarrheal morbidity. Bhandari et al. (1997) reported that, in children with acute diarrhea, a single 60-mg dose of vitamin A lowered the risk of persistent diarrhea.² Administering two doses of 200,000 IU of vitamin A at 6-month intervals to children in China significantly decreased the incidence of diarrhea (En-Lin et al. 1995, Lie et al. 1993), and the risk of getting diarrhea was 2.5 times lower among supplemented children than in unsupplemented ones (Lie et al. 1993). Similarly, supplementing children with 200,000 IU of vitamin A every 4 months for 1 year decreased the incidence of diarrheal episodes (Ross et al. 1995, Barreto et al. 1994). In South Africa, supplementation with up to 200,000 IU of vitamin A every 3 months reduced diarrheal morbidity in 1- to 15-month-old HIV-infected children but not among uninfected children (Coutsoudis et al. 1995b). A single dose of 200,000 IU of vitamin A decreased the incidence of diarrhea among children 1 to 5 years old during a 2-month follow-up period (Bloem et al. 1990a). Supplementation with 7500 IU of vitamin A per kg of body weight improved vision in vitamin A deficient patients with acute diarrhea a few days after supplementation (Molla et al. 1983).

Whereas the studies presented above have shown beneficial effects from vitamin A supplementation on the incidence or prevalence of diarrheal

² 1 mg = 1,000 μg ; 1 μg retinol = 1 retinol equivalent (RE) = 3.33 International Unit (IU) = 0.0035 μmol .

morbidity, several others have reported that supplementation with vitamin A, either as two or three high doses of 200,000 IU a year or as a weekly dose of 8333 IU, does not affect diarrheal morbidity. In a randomized community-based intervention trial, the prevalence of diarrhea was not significantly different among preschool children given two doses of 200,000 IU of vitamin A 6 months apart than in those who did not receive vitamin A (Abdeljaber et al. 1990). Similarly, Vijayaraghavan et al. (1990) found that one or two doses of 200,000 IU of vitamin A, given to children 1 to 5 years old, did not alter the risk of diarrhea. Another study, conducted in Indonesia, showed that supplementation with 206,000 IU of vitamin A given every 4 months did not affect the overall incidence of diarrhea (Dibley et al. 1996). The mean daily prevalence of diarrheal morbidity was also not altered by 4-monthly high-dose vitamin A supplementation for 1 year in Ghana (Arthur et al. 1992) or India (Ramakrishnan et al. 1995). The incidence of diarrhea was not affected by a weekly dose of 8333 IU of vitamin A for 1 year in children under 5 years old (Rahmathullah et al. 1991). Sinha et al. (1976) also reported that massive dose supplementation with vitamin A did not affect the rate of diarrhea in preschool children in West Bengal, India. In contrast to the above findings, Stansfield et al. (1993) reported an increased risk of diarrheal morbidity in preschool children with subclinical vitamin A deficiency after they received 200,000 IU of vitamin A every 4 months.

Of the four studies that looked specifically at the effect of vitamin A supplementation on morbidity, three found that supplementation had no effect on the incidence or prevalence of diarrhea (Bhandari et al. 1997, Arthur et al. 1992, Dibley et al. 1996), and one reported an effect on the incidence of moderate and severe diarrhea (Barreto et al. 1994). Three of the above studies looked at severe diarrhea and showed a beneficial effect of vitamin A supplementation. Bhandari et al. (1997) reported that vitamin A lowered the risk of persistent diarrhea (three or more loose or watery stools in 24 hours; diarrheal duration of ≤ 7 days) in children, although the mean duration of diarrhea and the number of stools passed did not change. Barreto et al. (1994) found that the benefit of 4-monthly megadose supplementation was greater among children with severe diarrhea (five or more liquid or semiliquid stools in 24 hours; diarrheal

duration of ≥ 3 days) than in children with mild or moderate diarrhea. In the Ghana VAST Health study, the overall incidence of severe diarrhea (six or more liquid or semiliquid stools on the worst day) was reduced by vitamin A supplementation (Ross et al. 1995). In contrast, Rahmathullah et al. (1991) found that the severity (≥ 1 day of four or more watery or loose stools per day) and duration of diarrhea were not affected by a weekly low dose of vitamin A; however, their trial was designed to look at the effect of supplementation on mortality rather than morbidity.

Two studies have looked at the effect of vitamin A therapy on acute diarrhea. In a randomized trial in South Africa, the severity of diarrheal morbidity was reduced and recovery was faster, although not statistically significant, when children were supplemented with three doses of up to 109 mg of vitamin A (Coutsoudis et al. 1991a). Similarly, a single dose of 200,000 IU of vitamin A given to children hospitalized for noncholera, watery diarrhea did not affect the duration or severity of the current diarrheal episode (Henning et al. 1992).

Confounding factors. Several factors may have contributed to the conflicting results of the controlled intervention trials on vitamin A supplementation and the incidence and prevalence of diarrheal morbidity. Although all the studies were controlled and randomized, error was embedded in them because of the need to use reported morbidity based on recall. Diarrheal morbidity was recorded either daily by parents (Pinnock et al. 1986) or immediate relatives of the children or by recall during daily or weekly visits by investigators. In some studies recall periods were even longer: reported morbidity was based on retrospective recall 2 and 4 months (Bloem et al. 1990a) or 3 months (Vijayaraghavan et al. 1990) after supplementation during the intervening period.

Another factor that may explain some of the varying results is the different age groups of children in the studies. Some studies were conducted on younger preschool children, whereas others had older preschool children as the subjects. It has been suggested that different cutoff values may be necessary to identify vitamin A deficiency status in younger versus older children (Lewis et al. 1990). In addition, the rates of diarrheal disease decrease with

age in children (Lie et al. 1993) and the benefits of vitamin A supplementation may be more apparent in younger children.

Yet another factor that may have contributed to the equivocal results of the controlled interventions is the feeding regimen of infants. In a recent study, the benefits of vitamin A supplementation were observed in non-breast-fed children but not in breast-fed children (Bhandari et al. 1997). Given that prolonged breast-feeding and delayed introduction of complementary foods is the norm for most young children in developing countries (Huffman and Martin 1994), suboptimal feeding patterns may have influenced the effect of vitamin A supplementation on diarrheal morbidity in at least some of the studies.

Lastly, different definitions for severity of diarrhea may be another error. For example, severe diarrhea was defined as having between two and six watery or loose stools per day and lasting 1 to 3 or more days.

Conclusion. Whether supplementation with vitamin A significantly reduces the incidence or duration of diarrheal morbidity is not clear, but it does reduce the severity of diarrhea. WHO (1988b) recommends distribution of 200,000 IU of vitamin A every 4 or 6 months to prevent xerophthalmia in children in countries where vitamin A deficiency is a public health problem. In a policy statement on vitamin A, diarrhea, and measles, The International Vitamin A Consultative Group (IVACG) “strongly recommends that vitamin A supplements be included in all child survival programs in areas of endemic vitamin A deficiency as a prophylactic and to lessen the consequences of diarrhea and measles” (IVACG 1996). The effectiveness of such an intervention in reducing diarrheal morbidity is not clear and needs to be established by future studies.

Measles-Associated Morbidity

One of the first studies to investigate the effect of vitamin A supplementation on measles-associated mortality and morbidity was conducted by Ellison (1932), who found that a daily dose of 300 IU of vitamin A for 1 to 3 weeks reduced the severity of pulmonary complications and the number of deaths attributed to measles in preschool children. Measles is now accepted as a risk factor for the development of severe vitamin A deficiency, because vitamin A

absorption is decreased, utilization is increased, and stores are depleted. Mobilization of vitamin A stores is also impaired during measles and supplementation with 200,000 IU of vitamin A improves vitamin A status (Coutsoudis et al. 1991b, Anonymous 1987, Sauter 1982). Thus, vitamin A therapy during measles significantly reduces the risk of blindness, postmeasles complications, and death (Fawzi et al. 1993, Sauter 1982, Barclay et al. 1987).

The joint WHO/UNICEF (1987) statement on vitamin A therapy during measles recommends oral administration of 100,000 IU of vitamin A to children under 1 year old and 200,000 IU of vitamin A to children above the age of 1 year. It further recommends that “vitamin A supplementation be provided to all children diagnosed with measles in communities in which vitamin A deficiency is a problem.” If any ocular signs of vitamin A deficiency are present, the initial dose should be repeated the next day and again 1 to 4 weeks later (Anonymous 1987).

Several investigations have evaluated the effect of the WHO recommended vitamin A dose in measles and the effect of periodic distribution of 200,000 IU every 4 or 6 months to children in communities where vitamin A deficiency is a public health problem. The results of these investigations are mixed, although most point to a beneficial effect of vitamin A supplementation.

Coutsoudis et al. (1992) observed a significant reduction in morbidity during both the acute and chronic phases of measles among children under 2 years old after administration of four doses of 200,000 IU of vitamin A. Measles-associated morbidity was also not affected by 210 mmol (200,000 IU) of vitamin A in 5-month-old to 17-year-old Zambian children (Rosales et al. 1996, Rosales and Kjolhede 1994). Hussey and Klein (1993) investigated the effects of both standard (200,000 IU) and high-dose (400,000 IU) vitamin A therapy on the incidence and severity of measles in children under 15 years old. Compared with children on standard therapy, those receiving high-dose vitamin A therapy had a shorter hospital stay, lower incidence of intensive care, and a lower mortality rate; no adverse effects from high-dose vitamin A therapy were observed.

In terms of the prophylactic effect of vitamin A on measles outcome, Dollimore et al. (1997) reported that there was no effect. In a large-scale

randomized trial in Ghana, the incidence of measles (and the case-specific fatality rate) was not significantly affected by vitamin A supplementation.

Based on the results of controlled intervention trials, Hussey and Klein (1993), Coutsoydis et al. (1991a), and Coutsoydis et al. (1991b) recommended that vitamin A supplements be administered to all children with severe measles, even where vitamin A deficiency is not a recognized public health problem. This view was supported by a meta-analysis of the controlled trials on vitamin A supplementation and childhood mortality, which found a strong protective effect of vitamin A against mortality from measles. These results led to the conclusion that vitamin A supplements should be given to all measles patients in developing countries whatever their vitamin A status (Fawzi et al. 1993).

Conclusion. UNICEF (1991) estimated that over 1.5 million children in developing countries die of measles each year. ***Vitamin A supplementation during measles has been shown to reduce measles complications, including blindness, and measles-associated mortality.*** Given the strong evidence for a beneficial role of vitamin A during measles, WHO recommends vitamin A therapy (up to 200,000 IU) for all children infected with measles in communities where vitamin A deficiency is prevalent.

Morbidity from Respiratory Illness

Case-control studies found that respiratory infections were more prevalent among children with xerophthalmia than in those without xerophthalmia and the prevalence appeared to increase with the severity of xerophthalmia (Sommer et al. 1984). These results have been confirmed by controlled intervention trials.

Dowell et al. (1996) reported that supplementation with up to 200,000 IU of vitamin A in children with respiratory syncytial virus infection resulted in a more rapid resolution of tachypnea (increased rate of respiration), and a shorter duration of hospitalization, in those children with significant hypoxemia (blood oxygen saturation $\leq 90\%$). Bresee et al. (1996) observed that vitamin A supplementation reduced the duration of hospitalization; they also found that serum retinol levels were inversely related to the severity of illness in children with this respiratory virus. Pinnock et al. (1986) noted that, despite

having no effect on plasma retinol levels, vitamin A supplementation reduced respiratory symptoms in preschool children with a history of respiratory illness. Significant reductions in the incidence of respiratory disease were observed in children under 3 years old who were supplemented with 200,000 IU of vitamin A at 6-month intervals (En-Lin et al. 1995, Lie et al. 1993). Bloem et al. (1990a) also observed that a single dose of 200,000 IU of vitamin A decreased the incidence of respiratory disease during a 2-month follow-up period.

Other studies have reported that vitamin A supplementation does not affect the vitamin A status or the incidence or severity of respiratory illness in children with respiratory disease. In India, supplementation with a single, double, or triple dose of 200,000 IU of vitamin A did not affect the incidence of respiratory illness in children under 5 years old (Ramakrishnan et al. 1995, Vijayaraghavan et al. 1990). Similar results were found in a randomized community trial in Brazil where, after administering the standard regimen of three doses of 200,000 IU of vitamin A per year, the incidence of acute lower respiratory illness among children under 4 years old did not change (Barreto et al. 1994). A single dose of 100,000 IU of vitamin A also did not affect the severity or duration of respiratory infection in children between the ages of 2 and 58 months (Quinlan and Hayani 1996). In India, 1 year of dosing children under 5 years old weekly with 8333 IU of vitamin A did not affect the incidence, severity, and duration of respiratory infection (Rahmathullah et al. 1991). Pinnock et al. (1988) reported that a weekly dose of 4.2 mg of retinol for 1 year had no effect on plasma retinol or respiratory morbidity in children with bronchiolitis in infancy.

Two studies reported that vitamin A supplementation may have a harmful effect on respiratory infection, especially in children with adequate nutritional status. Dibley et al. (1996) found that 206,000 IU of vitamin A every 4 months increased the incidence of acute respiratory illness by 8% and acute lower respiratory illness by 39% in preschool children. The detrimental effect of vitamin A was most pronounced in children with adequate nutritional status. Conversely, vitamin A showed a protective trend in children who were chronically malnourished. Another study reported an increased risk of respiratory disease in children 6 months to 6.9 years

of age with subclinical vitamin A deficiency who were receiving 200,000 IU of vitamin A every 4 months (Stansfield et al. 1993).

Pandey et al. (1991) found that standard vitamin A supplementation with 200,000 IU every 4 months for 1 year reduced the rate of pneumonia cases by up to 33% and decreased the rate of overall mortality in children under 5 years old in Nepal. No other study on vitamin A supplementation, however, has shown an effect on the incidence of, or mortality from, pneumonia. A recent meta-analysis of the pooled data from 12 large-scale trials led to the conclusion that vitamin A supplementation had no significant effect on the incidence of pneumonia (Vitamin A and Pneumonia Working Group 1995).

Among the studies on vitamin A therapy and pneumonia, Velasquez-Melendez et al. (1995) showed that 200,000 IU of vitamin A did not affect the vitamin A status of children with pneumonia 1 week after supplementation. Whether an improvement in vitamin A status would have been achieved within 1 week after supplementation is not known. Fawzi et al. (1998a) reported that large doses of vitamin A (up to 200,000 IU) had no protective effect on the severity of pneumonia in hospitalized Tanzanian children. In fact, more deaths due to pneumonia occurred in the vitamin A supplemented group than in the control group. Similarly, Nacul et al. (1997) found that vitamin A supplementation (one or two doses of 100,000 IU to infants and one or two doses of 200,000 IU to children 1 to 4 years old), besides the standard treatment for childhood pneumonia, had no effect on the overall duration of pneumonia or on the incidence of adverse outcomes. The incidence of fever in children with pneumonia, however, was reduced. In a randomized trial in South Africa, three doses of 200,000 IU of vitamin A reduced the severity of respiratory tract infection and hastened recovery from pneumonia among children under 2 years old who were hospitalized with measles (Coutsoudis et al. 1991a).

Confounding factors. As with diarrheal morbidity, factors that may have contributed to conflicting results for the effect of supplementation on the incidence and prevalence of respiratory infection include the long recall periods in some studies (Vijayaraghavan et al. 1990, Bloem et al. 1990a) and the differences in the age groups of children partici-

pating in the studies. Bloem et al. (1990a) found that children 1 to 2 years old had a higher incidence of respiratory infection than older children. Additionally, the underlying vitamin A and/or overall nutritional status of the children may have influenced the response to vitamin A supplementation. Another factor that may be an important source of error was the definition of respiratory infections, including the precision with which respiratory rates were measured. Fewer precise measurements can result in misclassification of children with acute respiratory illness (Dibley et al. 1996).

Conclusion. Vitamin A supplementation and therapy do not have any benefit on the incidence or mortality from nonmeasles pneumonia. Whether there are specific benefits of vitamin A supplementation in upper respiratory infections is not clear at this time and further evaluation is needed. Some studies have found benefits from the standard high-dose vitamin A supplementation, but others found no effect or even a harmful effect in well-nourished children.

Helminthic Infections and Vitamin A Status

It has been reported that parasitic infections can reduce vitamin A absorption by as much as 70% (Sivakumar and Reddy 1975; Mahalanabis et al. 1976; Mahalanabis et al. 1979). In addition, the utilization of vitamin A is increased during parasitic infection. Sivakumar and Reddy (1975) noted that the beneficial effect of deworming on vitamin A absorption lasted at least 2 months after treatment with the antihelminthic.

The effect of concurrent vitamin A supplementation and deworming on improving vitamin A status and/or the risk of infection has been investigated in a few studies. Jalal et al. (1998) found that vitamin A status improved significantly in Indonesian children heavily infected with *Ascaris* who were dewormed and supplemented with β -carotene-rich food, compared with children supplemented with β -carotene-rich food and not dewormed.

In contrast, Tanumihardjo et al. (1996) showed that deworming *A. lumbricoides*-infected Indonesian children with 400 mg of albendazole alone did not improve vitamin A status, whereas supplementation with 200,000 IU of vitamin A alone significantly

improved vitamin A status. Deworming, followed by vitamin A supplementation, marginally improved vitamin A status in only two of the three groups of children tested. Similarly, Reddy et al. (1986c) found that, among Indian children in urban slums, there was no advantage in improving and maintaining serum retinol levels of 6-monthly concurrent deworming and high-dose vitamin A supplementation over high-dose vitamin A supplementation alone.

Conclusion. Few studies have looked at helminthic infection and vitamin A status and further research is needed to determine the effects of deworming and subsequent vitamin A supplementation on vitamin A status.

Malarial Morbidity

An association has been reported between malaria infection and vitamin A status (Filteau et al. 1993, Tabone et al. 1992, Galan et al. 1990, Sturchler et al. 1987). Results from animal studies suggest that vitamin A deficiency may aggravate malarial infection. Using a rat model, Stoltzfus et al. (1989) showed that vitamin A deficiency decreases the body's ability to recover from malaria but only when the deficiency and infection occur early in life and the infection is very severe. Krishnan et al. (1976) reported that vitamin A supplemented rats could better resist, and recover faster from, malarial infection than vitamin A deficient rats.

The effect of vitamin A supplementation on the incidence and severity of malarial infection was investigated by Binka et al. (1995) in a randomized trial in northern Ghana. Supplementing children 6 months to 5 years old with 200,000 IU of vitamin A every 4 months for 1 year did not affect the incidence of fever, malaria parasitemia rates, parasite densities, or rates of probable malarial illness.

Malaria accounts for many child deaths in sub-Saharan Africa (Binka et al. 1995). In 1992, about 106 million children under 5 years of age were at high risk of contracting malaria. The annual clinical cases and malaria deaths were estimated to be 53 to 160 million and 1 to 3 million, respectively (Sturchler et al. 1993). Although vitamin A deficiency is highly prevalent in these populations, the potential role of vitamin A in malarial infection is not known.

Conclusion. More studies are needed to show the effect of vitamin A deficiency, and subsequent vitamin A supplementation, on the incidence, severity, and case fatality rate of malaria in developing countries.

Tuberculosis

Because of its role in the immune response to infection, vitamin A may influence the occurrence or severity of tuberculosis. *In vitro* studies have shown the inhibition of mycobacterial replication and an increased resistance to *Mycobacterium tuberculosis* attributable to retinoic acid, a derivative of vitamin A, in human cell cultures (McMurray et al. 1990, Crowle and Ross 1989), which suggests an immunoprotective role for vitamin A against tuberculosis.

Vitamin A deficiency has been observed in patients with tuberculosis. Several cases of low serum levels of vitamin A and carotene in patients with pulmonary tuberculosis were reported in the 1960s (Smurova and Prokop'ev 1969, Ignatova and Prokop'ev 1966, Covacev and Salomone 1966, Prokop'ev 1966, Prokop'ev 1965). In South African children with pulmonary tuberculosis, plasma vitamin A was 62% below normal values and the severity of the disease was associated with low vitamin A levels (Hanekom et al. 1997). Treatment with large doses of vitamin A, however, did not affect the outcome of the disease (Hanekom et al. 1997).

A recent statement from the Global Tuberculosis Programme (WHO 1998a) highlighted the fact that Asia accounts for 64% of the world's notified tuberculosis cases, while a lethal combination of HIV and tuberculosis is leading to sharp increases in the tuberculosis epidemic, particularly in Africa. It is estimated that, unless effective action is taken, worldwide 70 million people will die from tuberculosis between now and the year 2020, as drug-resistant strains of tuberculosis emerge because of poorly managed programs.

Conclusion. Given the reemergence of tuberculosis as a major public health problem, understanding the role of vitamin A in tuberculosis and the benefits of vitamin A supplementation as an adjuvant to standard therapy to reduce the adverse outcomes of the disease is important.

Overall Morbidity

In a randomized trial in South Africa, the severity of overall morbidity was reduced and recovery from fever was faster, although not statistically significant, when children were supplemented with three doses of up to 109 mg of vitamin A (Coutsoudis et al. 1991a). The severity of illness episodes, measured as the rate of clinic attendances and the rate of hospital admissions, was significantly lowered by vitamin A supplementation (Arthur et al. 1992). The mean daily prevalence of vomiting was also lowered by 13% by 4-monthly high-dose vitamin A supplementation for 1 year in Ghana (Arthur et al. 1992).

Conclusion. Vitamin A supplementation appears to reduce general morbidity symptoms in children.

Conclusion

Vitamin A deficiency is commonly found in the presence of infections and has been strongly associated with morbidity due to infections. Investigations of the effect of supplementation with vitamin A in improving morbidity symptoms, however, have provided equivocal results.

Vitamin A supplementation may reduce morbidity symptoms such as diarrhea, fever, and coughs. Given the strong evidence for a beneficial role of vitamin A during measles, WHO recommends vitamin A therapy (up to 200,000 IU) for all children infected with measles in areas where vitamin A deficiency is prevalent. Apart from measles-related respiratory infections, where there is a beneficial effect, the effects of vitamin A supplementation in respiratory diseases are conflicting: some studies have reported a beneficial effect of vitamin A supplementation and others have reported no effect or even a harmful effect of high-dose vitamin A therapy in well-nourished children. These results need to be evaluated further. The effects of vitamin A supplementation in parasitic and infectious diseases, such as tuberculosis, have not been thoroughly investigated.

4. ROLE OF VITAMIN A IN IMMUNITY

Several excellent reviews are available on the role of vitamin A in immune function and immune response in the presence of infection (Semba 1998, Semba 1994, Tomkins and Hussey 1989). This section provides a brief overview and summarizes the findings of the key studies (Annex Table 2). An explanation of the immunological terms used in this section is presented in Annex 2.

In vitro Studies with Human Cell Cultures

Recent *in vitro* studies with cord blood mononuclear cells and peripheral blood mononuclear cells have shown that vitamin A, in the form of retinol or retinoic acid, improves immunity by stimulating immunoglobulin synthesis through its action on T cells or T-cell products (Wang et al. 1993, Wang and Ballow 1993, Israel et al. 1991). In human thymocyte and tonsil lymphocyte cells, retinoic acid increased blastogenesis in response to mitogens (Sidell and Ramsdell 1988, Sidell et al. 1984, Sidell et al. 1981) but a similar proliferation was not observed in peripheral blood or spleen lymphocytes (Sidell and Ramsdell 1988, Sidell et al. 1981). Retinoic acid also inhibits the production of interleukin 6 in a dose-dependent manner by down-regulating the expression of interleukin 6 mRNA (Blomhoff et al. 1992, Sidell et al. 1991). Previously, *in vitro* experiments on immune responsiveness after extensive surgical treatment showed that pharmacological doses of vitamin A improve lymphocyte proliferation and mitogenic activity postoperatively (Cohen et al. 1979). Overall, these *in vitro* results suggest that vitamin A acts as an immunostimulant by modulating the growth and function of T cells and B lymphocytes.

Animal Experiments

Results of animal studies clearly show that vitamin A has a beneficial effect on immunity. Vitamin A deficient animals have impaired immune responses in

the presence of infection (Gangopadhyay et al. 1996), especially during severe infection (Stephensen et al. 1996). Vitamin A deficient animals have reduced antibody responses, which are normalized by supplementation with vitamin A, when challenged with antigens including tetanus toxoid (Molrine et al. 1995, Kinoshita et al. 1991, Pasatiempo et al. 1990), pneumococcal polysaccharide (Pasatiempo et al. 1992, Pasatiempo et al. 1991), and protein antigens (Pasatiempo et al. 1990). These results have been observed in different strains of rats; male rats may be affected to a greater extent than females (Pasatiempo et al. 1989). Other researchers have reported a similar impairment of immune response to mitogens in vitamin A depleted animals (Smith et al. 1987, Smith and Hayes 1987, Butera and Krakowka 1986, Nauss et al. 1985, Ongsakul et al. 1985, Barnett 1982, Sirisinha et al. 1980, Nauss et al. 1979) and enhanced immunity in vitamin A replete animals (Hatchigian et al. 1989, Smith and Hayes 1987, Barnett 1983). Repletion studies show that retinoic acid is more active than retinol or retinyl esters in inducing an immune response in vitamin A deficient mice (Chun et al. 1992).

Natural killer cell activity [a measure of cell-mediated immunity (CMI)] is reduced in vitamin A depleted animals. This impairment is reversed and interferon activity is increased when the animals are replete with oral retinol (Bowman et al. 1990). Sklan et al. (1989) reported that T-lymphocyte proliferative responses were decreased in vitamin A deficient chicks and enhanced with increased vitamin A intake, confirming the findings of *in vitro* experiments. In addition, Friedman and Sklan (1989a, 1989b) found that the impairment of T-lymphocyte activity in vitamin A deficient chicks and rats occurred before any other signs of vitamin A deficiency appeared and was rapidly corrected by increasing retinol intake. Taken together, the results of animal experiments show that vitamin A improves the immune response to various antigens partially through its actions on CMI, an arm of the immune system.

Extremely high doses of vitamin A seem to have a harmful effect on immunity to infections. Long-term excess vitamin A intake impaired antigen-specific immune responses in chicks. This impairment appeared before any other signs of vitamin A toxicity were observed (Friedman et al. 1991, Friedman and Sklan 1989b). It should be noted, however, that these animals were given about 2000 times the recommended daily allowance of vitamin A for many days. Semba (1994) reviewed the evidence from animal studies that showed additional vitamin A supplementation to animals with adequate vitamin A status enhanced immune responses to antigens and improved resistance to infection and concluded that a negative effect of vitamin A on immunity has been shown only with extremely high doses administered for many days and that periodically administering high doses of vitamin A supplements to children, as recommended by WHO, is beneficial.

Vitamin A Deficiency and Impaired Immunity in Infection: Cross-Sectional Surveys

Low serum vitamin A levels have been reported to have detrimental effects on immunity in humans. Decreased levels of secretory immunoglobulin A in the saliva have been observed in vitamin A deficiency (Karalliedde et al. 1979) and in vitamin A deficient children with Down's syndrome (Palmer 1978). Mucosal immunity, the body's "front line" defense mechanism, is compromised in vitamin A deficiency (Semba 1994).

Additionally, vitamin A deficiency is accompanied by detrimental alterations in T-cell subpopulations. Children with xerophthalmia have fewer CD4 T cells and lower CD4/CD8 ratios, which indicates depressed immunity, than children without xerophthalmia (Semba et al. 1993b). Even mild vitamin A deficiency has been associated with a relatively depressed immune response (Semba et al. 1992).

The immune system is challenged in the presence of infection, and the occurrence of vitamin A deficiency along with infection is an additional impediment in the body's ability to mount an immune response. In a prospective study in Rwanda, Semba et al. (1996) found that children hospitalized with meningococcal meningitis had fewer CD8 T cells and more CD4 T cells than a known reference popu-

lation. Impairment of immune response to bacterial meningitis was greater with a higher degree of vitamin A deficiency (serum retinol, 0.60 mmol/L). Similarly, vitamin A deficiency (serum retinol, <1.05 mmol/L) was associated with an impaired immune response (lower CD4 counts) in both HIV-seropositive and HIV-seronegative adults (Semba et al. 1993a).

Vitamin A Supplementation and Improved Immunity: Controlled Intervention Studies

The findings of impaired immunity in vitamin A deficient populations were further corroborated by controlled intervention trials. Among infants under 6 months old, three doses of 15 mg of vitamin A supplementation at the time of diphtheria-pertussis-tetanus (DPT)/oral poliovirus vaccine (OPV) immunizations resulted in higher positive delayed cutaneous hypersensitivity tests (CMI) among those with adequate serum retinol. CMI response was consistently better in well-nourished infants regardless of vitamin A supplementation. Another study with 4- to 24-month-old infants showed that three doses of up to 200,000 IU of vitamin A resulted in an increase in total lymphocyte counts and immunoglobulin G (IgG) levels in children with measles (Coutsoudis et al. 1992). In children 6 to 36 months old, vitamin A supplementation (200,000 IU) enhanced immunity (measured as an increase in IgA levels) even 7 weeks after supplementation (Lie et al. 1993).

Among children 3 to 6 years old with clinical and subclinical vitamin A deficiency, 200,000 IU of vitamin A increased the numbers of circulating CD4 T cells and resulted in a higher CD4/CD8 ratio 5 weeks after supplementation (Semba et al. 1993b). When vitamin A was given 2 weeks before a tetanus vaccine, both primary and secondary IgG responses were increased more than 2-fold (Semba et al. 1992); this was mediated through an increase in the level of IgG1 (Semba et al. 1994b), a subclass of IgG usually involved in the protective antibody response to tetanus (Semba 1994). In contrast, Rosales and Kjolhede (1994) found that a single dose of 210 mmol (200,000 IU) of retinol as retinyl palmitate did not enhance the immune system in the presence of measles infection in children. A similar negligible effect of vitamin A on immune response to tetanus

toxoid was observed by Brown et al. (1980) in Bangladeshi children.

In adults, treatment with 13-*cis*-retinoic acid, a derivative of vitamin A, normalized the humoral immune response in common variable immunodeficiency patients (Saxon et al. 1993) and improved antibody response to antigen (keyhole limpet hemocyanin) in subjects with severe cystic acne (Sidell et al. 1990). Postoperative depression in lymphocyte numbers was also reversed by pharmacologic doses of vitamin A (Cohen et al. 1979).

Whether β -carotene, a precursor of vitamin A, also enhances the immune response is not clear. Two studies showed that β -carotene supplementation enhanced immune responses in immunocompetent adults (Alexander et al. 1985) and in HIV-positive patients (Coodley et al. 1993b), whereas another study revealed that β -carotene did not influence immune cell counts in HIV-infected patients (Coodley et al. 1996). Given that the dose of β -

carotene (180 mg) was the same in two of the studies and both included HIV-infected subjects (Coodley et al. 1996, Coodley et al. 1993b), other factors need to be identified that may explain the conflicting results.

The findings of the above cross-sectional and controlled intervention studies show a key role for vitamin A in the body's response to infection. Evidence suggests that vitamin A deficiency diminishes, whereas supplementation with vitamin A enhances, immune response to infection in humans.

Conclusion

It is well known that vitamin A deficiency is commonly observed during infection and is associated with increased morbidity and mortality in humans, especially in infancy and childhood. This may be partially explained by the important role of vitamin A in mucosal, cell-mediated, and humoral immunity and ultimately in developing an immune response to infection.

5. EFFECT OF VITAMIN A IN HIV INFECTION AND TRANSMISSION

The role of vitamin A in HIV infection is now becoming known, although many questions remain unanswered. In adults, adequate vitamin A status appears to help protect against the progression of HIV, the extent of viral load, and survival of HIV patients. In pregnant mothers and infants, evidence is surfacing to show that vitamin A plays a role in limiting the transmission of HIV from mother to infant, the extent of the HIV viral load in the breast milk of HIV-infected women, and the health and survival of infants born to HIV-infected mothers. The role of vitamins, including vitamin A, in HIV disease progression and transmission has recently been reviewed by Fawzi and Hunter (1998).

Cross-Sectional Surveys

Twelve cross-sectional studies, some of which are case-controlled, investigating the role of vitamin A in HIV/AIDS are tabulated in Annex Table 3.

Vitamin A Status and Transmission of HIV from Mother to Infant

Findings from cross-sectional surveys, one conducted in the United States (Greenberg et al. 1997), two in Kenya (Mostad et al. 1997, Nduati et al. 1995), and one in Malawi (Semba et al. 1994a), suggest that maternal vitamin A status is indirectly linked to transmission of HIV from mother to infant.

Greenberg et al. (1997) compared serum vitamin A levels in the third trimester of pregnancy in mothers transmitting HIV with nontransmitting mothers and found that severe vitamin A deficiency was more prevalent among transmitting mothers than in nontransmitting ones. Similarly, Semba et al. (1994a) reported that mothers who transmitted HIV to their infants had lower serum vitamin A levels than mothers who did not. Maternal transmission rates increased as serum vitamin A levels decreased; a

32.4% transmission rate was associated with serum retinol $< 0.70 \mu\text{mol/L}$. In both studies, the adverse relationship between vitamin A deficiency and HIV transmission persisted, even after adjustments were made for confounding factors including CD4 lymphocytes.

Transmission of HIV-1 through vaginal shedding or breast milk has also been linked with vitamin A status. Nduati et al. (1995) found that severe vitamin A deficiency was associated with a 20-fold increase in the risk of HIV-1 DNA in breast milk, especially in women with low CD4 lymphocyte levels. Mostad et al. (1997) and John et al. (1997) independently reported that vitamin A deficiency was highly predictive of vaginal HIV-1 DNA shedding, which suggests that vitamin A status may be an important factor in vertical or sexual transmission of HIV. These findings provide a further basis for maintaining adequate vitamin A status during pregnancy.

Maternal Vitamin A Status and Health and Survival of Infants

Maternal vitamin A deficiency among HIV-infected mothers has been shown both to increase the rate of transmission of HIV and to affect the health and survival of their infants adversely.

In a longitudinal study in Malawi, Semba et al. (1997c) found that, after adjusting for confounding factors, including gender and body mass index, maternal vitamin A deficiency was related to linear and ponderal growth of children. At 1 year of age, children of vitamin A deficient mothers were shorter and lighter than children of nondeficient mothers. In another study in Malawi by Semba et al. (1995b), maternal vitamin A status was indirectly related to infant mortality rates, with the highest rates (93.3%) among mothers with the lowest serum vitamin A levels ($< 0.35 \text{ mmol/L}$).

Vitamin A Status in HIV Patients and Its Relation to Progression to AIDS

In nonpregnant, HIV-infected adults, vitamin A deficiency has been implicated in several adverse health effects including wasting (Coodley et al. 1993a), decreased immunity (Jolly et al. 1997, Semba et al. 1993a), and even death (Semba et al. 1995a, Semba et al. 1993a).

The presence of HIV infection causes a severe burden on the body stores of several nutrients (Beach et al. 1992) including vitamin A. HIV patients have been reported to have inadequate vitamin A stores and vitamin A deficiency appears to be highly prevalent among HIV-infected adults (Semba et al. 1993a, Coodley et al. 1993a, Beach et al. 1992).

Although vitamin A deficiency is apparently common and is associated with wasting among HIV-infected patients, its association with viral load and progression to AIDS is unclear. Semba et al. (1997b) found that, despite >28% prevalence of vitamin A deficiency among HIV-infected adult users of injected drugs, plasma vitamin A levels were not significantly correlated with infectious viral loads in these people. Although vitamin A deficiency appears to be an important risk factor in HIV progression, based on findings of increased prevalence of vitamin A deficiency, decreased immunity, and increased risk of death, Tang et al. (1997) found no consistent relationship between serum vitamin A levels and the risk of progression to AIDS. They also did not find an association between vitamin A status and CD4 cell counts (a measure of immune response) among these subjects. Conversely, a moderately high dietary intake of vitamin A (9000 to 20,000 IU/day) has been associated with reduced progression to AIDS among HIV-infected homosexual men (Tang et al. 1993).

Controlled Intervention Studies

The role of vitamin A and its precursor, β -carotene, in HIV infection has also been investigated in controlled intervention trials, eight of which are tabulated in Annex Table 3. These studies looked at the effect of β -carotene supplementation on infectious viral loads in HIV-infected adults, the effect of vitamin A supplementation on immune response in HIV-infected adults, and the effect vitamin A supplementation on the health of infants of HIV-infected mothers.

Effect of Vitamin A Supplementation on Viral Load

Intervention studies investigating whether vitamin A supplementation has beneficial effects on patients by decreasing viral loads in HIV infection have produced conflicting results. Semba et al. (1998) found that a single dose of 200,000 IU of vitamin A did not have a significant effect on HIV load 2 or 4 weeks after supplementation among HIV-infected users of injected drugs. In a randomized trial in South Africa, however, Coutsooudis et al. (1997) found that daily supplementation with 5000 IU of vitamin A (along with 30 mg of β -carotene) from 28 weeks of gestation until delivery inhibited the increase in viral load observed in nonsupplemented women. These results have significant implications in reducing vertical transmission of HIV, and consequently the health of the infant, and need to be investigated further.

Effect of β -Carotene or Vitamin A Supplementation on Immunity

A high dietary intake of β -carotene is associated with improved survival (a relative hazard of 0.60) in HIV-1-infected adults (Tang et al. 1996). However, controlled intervention studies have provided conflicting results. One study showed that β -carotene supplementation enhanced the immune response in HIV-positive patients (Coodley et al. 1993b), but another found that β -carotene did not influence immune cell counts in HIV-infected patients (Coodley et al. 1996). Given that the dose of β -carotene was the same in both studies, other factors that may explain the conflicting results need to be identified.

Vitamin A supplementation has been shown to improve humoral immune systems among patients with common variable immunodeficiency (Saxon et al. 1993); however, its effect on immunity in HIV-infected patients is not clear. Although cross-sectional surveys have linked vitamin A deficiency with decreased immune responses in HIV infection, a recent controlled intervention study found that supplementation with vitamin A (5000 IU/day) and β -carotene (30 mg/day) together did not affect T-cell counts in pregnant women (Fawzi et al. 1998b). More controlled studies are needed to establish the effect of vitamin A supplementation on immune responses in the presence of HIV infection.

Effect of Vitamin A Supplementation on Infant Health

Maternal vitamin A deficiency has been associated with increased infant and perinatal mortality among offspring of HIV-infected women (Dushimimana et al. 1992). Whether maternal vitamin A supplementation has a beneficial effect on infant morbidity and mortality among HIV-infected mothers, as it does in the non-HIV-infected vitamin A deficient population, is currently being evaluated. Recently, Fawzi et al. (1998b) reported that maternal vitamin A supplementation (5000 IU along with 30 mg of β -carotene daily) had no effect on the birth weight, risk of preterm delivery, or other birth outcomes among HIV-infected Tanzanian women. In contrast, supplementation with multivitamins (a total of eight vitamins) decreased the risk of preterm delivery, small size for gestation age, and low birth weight among these women. The authors speculated that poor absorption and increased requirements for vitamin A in HIV-infected subjects may have contributed to the lack of effect of vitamin A, and higher doses of vitamin A may prove beneficial.

A randomized trial in South Africa revealed that vitamin A supplementation (up to 200,000 IU every 3 months) of 1- to 15-month-old children significantly reduced diarrheal morbidity among HIV-infected, but not uninfected, children (Coutsoudis et al. 1995b). Results from four other vitamin A supplementation trials ongoing in Malawi, South Africa, Zimbabwe, and Nepal are currently awaited. As these results become available, a clearer picture of a beneficial or a negligible effect of maternal vitamin A supplementation on infant health and survival in HIV-infected mothers may be obtained.

Conclusion

One of the problems in interpreting work in this area is that serum retinol is altered by the acute-phase response to infection, and its use as an indicator of vitamin A status in HIV-infected subjects is questionable. Many studies cited here have used serum retinol as an indicator of vitamin A deficiency, and these results may have to be treated with caution. Moreover, the cutoff level of serum retinol used to detect vitamin A deficiency in HIV-infected patients is still being debated (Rosales and Ross 1996).

The data from cross-sectional surveys presented above are somewhat consistent and portray a beneficial role of vitamin A in the presence of HIV infection. Vitamin A deficiency is associated with an increased rate of transmission of HIV from mother to infant; decreased growth and increased risk of mortality in infants; and impaired immunity, wasting, and increased risk of death in adults. However, these findings have not been proved through controlled intervention trials. So far, vitamin A supplementation studies provide conflicting data on the role of vitamin A in enhancing immunity, controlling viral load, and promoting the health of mother and infant in the presence of HIV infection. These issues need to be resolved before a beneficial effect of vitamin A supplementation can be established and policy or program recommendations considered.

For this reason, future research needs to include establishing a uniform cutoff level of serum retinol that shows vitamin A deficiency or developing an alternative indicator(s) that better predicts vitamin A status in the presence of infection.

6. VITAMIN A ADMINISTRATION AND IMMUNIZATION: EFFICACY AND SAFETY

Among the 78 countries where vitamin A deficiency has been documented as a public health problem, 61 have policies and programs for widespread distribution of vitamin A supplements to children every 4 to 6 months beginning at 6 months of age (Micronutrient Initiative 1998). Vitamin A coverage, however, in most countries has not reached the target level of 80%. In contrast, much higher success rates have been achieved for child immunization; thus, including vitamin A as part of the Expanded Program of Immunization is being considered as a means to deliver supplements to young children. Indeed, it has been suggested to be a cost-effective approach to achieving adequate vitamin A status in children (Arhin et al. 1993).

WHO recommends that in developing countries 100,000 IU of vitamin A be given to infants between the ages of 6 and 12 months at the time of immunization (WHO/UNICEF 1993). The lack of information on both the safety of concurrently administering vitamin A with vaccination and the effect of a high dose of vitamin A on the efficacy of vaccines has been a constraint to the acceptance and widespread application of this approach.

Effect of Vitamin A on Efficacy of Measles Vaccine: Controlled Intervention Studies

Four controlled intervention studies have looked at the effect of vitamin A on the efficacy of measles vaccine (Annex Table 4). Factors evaluated included administration of 100,000 IU of vitamin A along with measles vaccine as a single dose versus two doses and the age at administration (6 months, 9 months, or both 6 and 9 months).

In Indonesia, Semba et al. (1995c) found that 100,000 IU of vitamin A at the time of measles immunization at 6 months of age lowered the rate of seroconversion only in infants who still had maternally acquired antibodies. On the other hand, vitamin A did not affect seroconversion in infants

who did not have detectable maternal antibody. In a clinical trial in Guinea-Bissau, Stabell-Benn et al. (1995a) found that concurrent administration of 100,000 IU of vitamin A with measles vaccine at 6 months of age did not affect seroconversion or interfere with measles immunity.

More recently, Semba et al. (1997a) reported that in Indonesia 100,000 IU of vitamin A given at the time of measles vaccination to infants 9 months of age did not affect seroconversion to live measles vaccine. Stabell-Benn et al. (1997) confirmed these results in a clinical trial in Guinea-Bissau, in which simultaneous administration of vitamin A and measles vaccine at 6 months or at 6 and 9 months did not show any negative effect on measles immunity. They further reported that, among children who received only one dose of measles vaccine at 9 months, vitamin A increased antibody concentrations, especially in boys, which suggests that vitamin A supplements may exert a stronger effect the later the children are immunized.

Taken together, the findings of the above studies show conclusively that vitamin A supplementation at the time of measles vaccination, whether as a single dose at 9 months of age or as a two-dose measles vaccine schedule at 6 and 9 months of age, is safe and does not interfere with measles immunity (Ross and Cutts 1997).

Safety of Administering Vitamin A Along with Vaccines: Controlled Intervention Studies

The safety of administering vitamin A with vaccines has been tested in four controlled intervention trials (Annex Table 4). Vitamin A doses ranged from 75,000 to 200,000 IU and were given along with DPT/OPV or measles vaccine.

De Francisco et al. (1993) reported that three doses of 50,000 IU of vitamin A given at 6, 10, and 14 weeks of age along with DPT/OPV immunization

resulted in episodes of bulging fontanelle in about 10% of infants, with a trend toward a cumulative effect of toxicity with increasing doses. Similar findings were reported by Baqui et al. (1995) and Rahman et al. (1995) in infants who received three doses of 25,000 IU of vitamin A at 6.2, 11.8, and 17.0 weeks of age along with DPT/OPV immunizations. About 85% of the episodes of bulging fontanelle occurred in infants who received vitamin A along with vaccines; the number of episodes increased with an increasing number of vitamin A doses, which suggests a cumulative vitamin A effect (Baqui et al. 1995). In the study by Rahman et al. (1995), more infants who received vitamin A developed bulging fontanelle than those not receiving vitamin A along with the vaccines. In all the above studies, the fontanelle bulging episodes were transient, resolved in 24 to 48 hours, and were not associated with any neurological signs or symptoms.

In contrast, Stabell-Benn et al. (1995a) reported the absence of bulging of the fontanelle among infants supplemented with two doses of 100,000 IU of vitamin A, one at 6 months and the other at 9 months of age, administered along with measles vaccine.

A recent multicenter randomized trial assessed the benefits and safety of three doses of 25,000 IU of vitamin A supplementation linked to DPT/OPV immunization 6, 10, and 14 weeks after postpartum vitamin A supplementation. A larger proportion of vitamin A than placebo recipients had bulging fontanelle within 48 hours of administration, although fewer than 1% in either group were affected. This level is lower than the 10% reported by de Francisco et al. (1993) and Baqui et al. (1995). The regimen used in the multicenter trial had no effect on overall or severe morbidity during the first 9 months of life. There were no differences in vitamin A status at the time the infants received the first dose or at ages 9 and 12 months; however, at 6 months, vitamin A status of the supplemented group was better than that of controls, which indicates that the regimen used was beneficial only up to 6 months of age (WHO/CHD [child health division] Immunisation-Linked Vitamin A Supplementation Study Group 1998).

Confounding factors. The varying results of the above studies may be explained by the difference in

the type of vaccines and the difference in the age of children at the time of vitamin A supplementation. A single dose of 50,000 IU of vitamin A to newborns caused bulging fontanelle within 24 hours after administration; however, intracranial pressure did not increase (Agoestina et al. 1994). DPT and DT vaccines have also been shown independently to cause bulging fontanelle in infants (Gross et al. 1989). Thus, vitamin A and DPT vaccines given together may be expected to cause bulging fontanelle in the studies by de Francisco et al., Baqui et al., and Rahman et al. The interactions between vitamin A and the different vaccines have not been studied. Vitamin A interaction with DPT vaccines may differ from its interaction with measles vaccine, which may explain the absence of bulging fontanelle when vitamin A was given with measles vaccine.

Another important factor is the age of the infant. In all three studies that reported bulging fontanelles, vitamin A was administered within 17 weeks (about 4 months) of birth. In contrast, in the study by Stabell-Benn et al. (1995a) that reported no incidence of bulging fontanelle in infants, vitamin A was administered at 6 months of age followed by a second dose 3 months later. The older infants may have had some protection against the effect of vitamin A and/or vaccine on their intracranial volume. Moreover, the fontanelles may be closed in some children at this age.

Conclusion

Overall, four controlled trials show that administering a total dose of 75,000 to 150,000 IU of vitamin A along with DPT vaccines may have a negative, cumulative effect in infants 4 months old. However, 200,000 IU of vitamin A given in two doses, one at 6 months and the other at 9 months of age, along with measles vaccine is safe without increasing the risk of developing bulging fontanelles.

Administering 100,000 IU of vitamin A along with measles vaccine, at 6 months of age or at 6 and 9 months of age, does not interfere with the efficacy of measles vaccine and is safe. Until future studies suggest otherwise, the current WHO recommendation of administering 100,000 IU of vitamin A to infants between the ages of 6 and 12 months at the time of measles immunization needs to be actively

promoted, carried out, monitored, and evaluated in developing countries.

Postpartum vitamin A supplementation followed by concurrent vitamin A supplementation (25,000 IU) with DPT/OPV immunization is also safe but does not show any sustained benefits beyond 6 months of age.

7. SAFETY OF VITAMIN A DURING PREGNANCY

The functions of vitamin A in reproduction and fetal development are well established. It is known that vitamin A deficiency adversely affects reproductive function in humans and several animal species (Sharma and Misra 1988, Sharma and Misra 1987, Underwood 1984). Vitamin A levels are significantly lower in preterm than in full-term infants and serum retinol is positively correlated with the birth weight of infants (Coutsoudis et al. 1995a). Debate continues, however, about the safety of vitamin A supplementation during pregnancy. Although there is a consensus that a deficiency or excess of vitamin A is harmful during pregnancy, there is no agreement about the definition of excess or about the level above which vitamin A may be unsafe.

The Teratology Society (1987) recommended limiting vitamin A in prenatal multivitamin preparations from 5000 to 8000 IU/day, as the teratogenic effect of vitamin A appears to occur at an undetermined level above 8000 IU/day. Vitamin A is especially harmful during early pregnancy when organogenesis occurs. The Teratology Society also recommended the US recommended daily intake of 8000 IU/day for pregnant women as the maximum vitamin A intake before and during pregnancy. Similar recommendations have been independently made by the Council for Responsible Nutrition (1987) and the Centers for Disease Control (Costas et al. 1987). The American College of Obstetricians and Gynecologists (1993) recommends the lower level of 5000 IU/day as the maximum intake before and during pregnancy. The above recommendations, however, are for the US population, whose dietary (natural and fortified sources) and pharmaceutical vitamin A intakes are higher than those of women in developing countries.

WHO (1998b) recommends that, where vitamin A deficiency is endemic, a maximum of 10,000 IU/day or a total of 25,000 IU/week be given to pregnant women independent of their vitamin A status. No data are available on the safety of a weekly dose of 25,000 IU of vitamin A during pregnancy.

The rationale for the safe vitamin A dose during pregnancy has been based on findings from animal and human studies involving supplementation with vitamin A (retinol and retinyl esters) and its derivative, 13-*cis*-retinoic acid. Much of the knowledge about the toxicity of vitamin A in pregnancy arose from research with the drug isotretinoin, a *synthetic* form of 13-*cis*-retinoic acid, which was widely used in the treatment of severe cystic acne. Following reports of congenital defects in children born to women who received the drug during pregnancy, several animal experiments and case-control studies were conducted to confirm the toxicity of 13-*cis*-retinoic acid during pregnancy (Rosa et al. 1986, Lammer et al. 1985). The adverse effects observed were particularly significant during early pregnancy when 13-*cis*-retinoic acid interferes with formation and development of vital organs, leading to severe birth defects.

Animal Experiments

Animal experiments conducted to test the safety of vitamin A revealed that exposure to high teratogenic doses of vitamin A during pregnancy led to congenital malformations in offspring (Vorhees et al. 1978, Vacca and Hutchings 1977, Palludan 1976) (Annex Table 5). Despite interspecies variation in sensitivity to vitamin A teratogenicity, a characteristic pattern of malformation is observed: craniofacial, eye, ear, cardiovascular, urogenital, and limb anomalies. For ethical reasons, these findings cannot be confirmed by case-control or epidemiological studies in humans.

The following sections discuss case reports, case-control studies, and controlled intervention studies on the toxicity of vitamin A at high doses (above 10,000 IU/day) and the safety of vitamin A at levels recommended for daily use (8000 IU/day) during pregnancy.

Case Reports

Several case reports have been published on the toxicity of vitamin A at high doses during pregnancy (Roche Vitamin A Working Group 1993, Von Lennep et al. 1985, Strange et al. 1978, Mounoud et al. 1975, Bernhardt and Dorsey 1974, Pilotti and Scorta 1965) and they are presented in Annex Table 5. The vitamin A levels in these cases ranged from 25,000 to 150,000 IU taken daily over a few days to months during the first trimester of pregnancy.

Rosa et al. (1986) analyzed 18 case reports (5 published and 13 unpublished cases) of birth defect outcomes of pregnancies with high-dose vitamin A exposure. Although epidemiological data in humans are not available to confirm the case reports, the authors concluded that, given the results of animal experiments with vitamin A and human studies with isotretinoin, avoiding long-term high-dose vitamin A use among fertile women is prudent.

In contrast, the Roche Vitamin A Working Group (1993) presented a different interpretation of a critical evaluation of these case reports. The medical and nutritional histories of cases reported were incomplete and, given the inherent retrospective nature of case reports, the author determined that there is no conclusive evidence to link vitamin A use during pregnancy to birth defects.

Case-Control Studies and Cross-Sectional Surveys

Seventeen population-based or hospital-based case-control studies or reanalysis of data from such studies have been published (Annex Table 5). Five cross-sectional surveys on vitamin A status and pregnancy outcomes are also tabulated in Annex Table 5.

Overall, several factors have been considered in the experimental design of these studies: time of administration of vitamin A (periconception period—that is, at least 1 month before conception to at least the second missed period, second trimester, third trimester, or entire pregnancy), dose of vitamin A (up to 8000 IU/day, 8000 to 10,000 IU/day, >10,000 IU/day, and >25,000 IU/day), type of birth defects [cranial-neural-crest defects, orofacial clefts, conotruncal heart defects, limb anomalies, and neural tube defects (NTDs)], and mode of vitamin A consumption (as single vitamin A supplements or as multivitamin supplements containing vitamin A).

Pregnant women enrolled in the studies were followed until the end of the pregnancy and the outcome of pregnancy was recorded. Women were interviewed for medical history, diet history, and use of vitamin supplements and medications during pregnancy. The data were assessed for a correlation between vitamin A or multivitamin supplement intake and pregnancy outcomes, while adjusting for confounding factors such as medical history, socioeconomic status, and so forth.

The major findings of these studies were as follows:

- Women who consumed vitamin A at levels above 10,000 IU/day from single vitamin A supplements were at an increased risk of delivering infants with congenital cranial-neural-crest and other birth defects; the risk of having infants with birth defects was even higher at levels above 40,000 IU/day (Rothman et al. 1995, Martinez-Frias and Salvador 1990, Werler et al. 1990, Rosa et al. 1986).
- The period of gestation when exposure to high doses of vitamin A occurs was related to the degree of risk of birth defects; the risk was estimated to be higher when exposure occurred in the first and/or second month of pregnancy rather than in later months (Rothman et al. 1995, Martinez-Frias and Salvador 1990, Werler et al. 1990).
- Multivitamin supplementation during the periconceptional period or at some time during pregnancy either reduced the risk of having infants with NTDs, limb anomalies, conotruncal heart defects, central nervous system defects, or other major birth defects (Yang et al. 1997, Khoury et al. 1996, Botto et al. 1996, Shaw et al. 1995a, Shaw et al. 1995b, Werler and Mitchell 1993, Werler et al. 1990, Milunsky et al. 1989, Mulinare et al. 1988, Costas et al. 1987, Winship et al. 1984) or did not alter the risk of birth defects (Mills et al. 1989). Multivitamin preparations (sold in the United States and used in the above studies) contain an estimated 3000 to 10,000 IU of vitamin A per tablet, showing that this dose of vitamin A did not increase the risk of birth defects and can be considered safe during pregnancy.
- Vitamin A supplement use during the periconceptional period was not associated with an increased risk of orofacial clefts (Shaw et al. 1996) or other major birth defects (Mills et al.

1997) at levels of 8000 to 10,000 IU/day. The threshold for supplemental vitamin A during pregnancy appears to lie near 10,000 IU/day (Rothman et al. 1995).

- Hyporetinemia in the mother or infant has been associated with preterm delivery (Peeples et al. 1991), low birth weight (Hussein et al. 1988), and perinatal mortality (Gebre-Medhin and Vahlquist 1984).

The study of Zuber et al. (1987) is the only one to report that high doses (>25,000 IU/day) of vitamin A were not harmful during pregnancy. Among 27 pregnant women, those taking high doses (>25,000 IU/day) of vitamin A were not at increased risk of having infants with congenital defects.

Controlled Intervention Studies

Many studies involving the use of multivitamin supplements that contain up to 8000 IU of vitamin A have shown the beneficial effects of multivitamins on reducing the risk of birth defects. They also provide evidence for the safety of vitamin A at 4000 to 8000 IU/day during pregnancy.

Twelve published, randomized, placebo-controlled intervention trials are presented in Annex Table 5. Eleven of these trials aimed at determining the efficacy of supplementation of pregnant women with multivitamins containing folic acid in reducing the risk of NTDs; these multivitamins contained an estimated 4000 to 8000 IU of vitamin A per tablet. One study investigated the safety of a single dose of 50,000 IU of vitamin A administered to neonates and found this level to be safe (Agoestina et al. 1994). No intervention studies on the safety or efficacy of vitamin A in pregnant women were found.

All 11 intervention trials with multivitamin supplements found that supplementation during the periconceptional period or at some period during pregnancy significantly decreased the risk of occurrence of NTDs or the recurrence of NTDs in women with a history of NTD births. Given that these multivitamins also contained vitamin A, it can be deduced that the level of vitamin A found in multivitamins (up to 8000 IU) is safe and presents no risk of birth defects.

Limitations

The results presented above need to be considered in light of the limitations of the studies, some inherent to the type of study and others specific to the design of the trial. Whereas findings from animal studies suggest the safety or efficacy of vitamin A within a physiological system, they cannot be extrapolated to humans. Among other factors, considerable interspecies differences in sensitivity to vitamin A teratogenicity make it difficult to directly relate animal data to humans.

The case reports presented are missing several pieces of critical information, including the nutritional and obstetrical history of the mothers, duration of vitamin A administration, and information about other medications taken concomitantly.

Case-control studies rely heavily on the ability of women to recall dietary and medical information. Mothers were interviewed several months after delivery about the period before and during pregnancy. Another limitation of the prospective studies was the small number of cases compared with a much larger number of controls, making it difficult to establish a causal relationship versus a correlation or association. Additionally, very few women were identified as consuming high doses (>25,000 or >40,000 IU/day) of vitamin A; thus, there was no statistical significance for these findings.

In contrast to case-control studies, controlled intervention trials can establish a direct relationship between vitamin A and pregnancy outcome. For obvious ethical reasons, there have been no interventions with potentially harmful high doses of vitamin A. All intervention studies presented focus on multivitamin supplements, rather than vitamin A alone, and the vitamin A content of these supplements was only an estimate.

Despite these limitations, the results of the case-control and controlled intervention trials provide conclusive evidence about the safety of vitamin A at a level (8000 IU/day) recommended during pregnancy. Programs aimed at reducing the adverse effects of vitamin A deficiency on maternal and neonatal health through administration of vitamin A supplements before or during pregnancy generally conform to the recommended level and should continue to do so.

Conclusion

Current scientific evidence, based on data from developed countries where vitamin A intakes are much higher than in developing countries, suggests that vitamin A supplementation before or during pregnancy should be limited to no more than 8000 IU/day, although up to 10,000 IU/day appears to be safe. Vitamin A intakes above 10,000 IU/day during pregnancy, especially early pregnancy, may cause major birth defects and are considered harmful. Vitamin A supplementation programs should adhere to these recommendations.

8. EFFECT OF VITAMIN A DURING LACTATION

Newborns have marginal vitamin A stores; theoretically, they depend on vitamin A intake through breast milk during the first 6 months of life to meet their vitamin A requirements. Because of poor dietary intakes of vitamin A, many women in developing countries enter pregnancy, and subsequently the lactation period, with marginal to inadequate vitamin A status. Infants born to these mothers are not protected against vitamin A deficiency, which has severe health implications ranging from increased risk of morbidity, infectious diseases, and even mortality.

Cross-Sectional and Controlled Intervention Studies

The close relationship between maternal vitamin A intake and the vitamin A content of breast milk has been established through cross-sectional comparative surveys (Brown et al. 1986, Gebre-Medhin et al. 1976) and controlled intervention studies (Bates 1983, Kon and Mawson 1950) (Annex Table 6). The subject has been reviewed by Bates (1983) and Rodriguez and Irwin (1972). The proportional increase in breast milk retinol in relation to vitamin A intake has been confirmed by two tightly controlled, randomized, intervention trials (Roy et al. 1997, Stoltzfus et al. 1993).

Given the importance of adequate vitamin A status in newborns, and the poor protection offered to them through breast milk from mothers whose vitamin A status is compromised, an intervention to supplement these mothers with a single high dose of vitamin A after childbirth appears justified. Controlled intervention trials conducted by Roy et al. (1997) and Stoltzfus et al. (1993) suggest that postpartum supplementation of mothers with about

200,000 IU of vitamin A increases maternal serum and breast milk retinol for up to 6 and 8 months, respectively, after supplementation. Additionally, this type of supplementation enhances the vitamin A status of infants for up to 6 months (Stoltzfus et al. 1993) and reduces the severity of respiratory tract infection and the incidence of febrile illness in the infants (Roy et al. 1997). A similar study that is currently under way in Zimbabwe (Roy et al. 1997) will provide additional information on the efficacy of postpartum vitamin A supplementation.

The WHO multicenter randomized trial (Annex Table 4) of postpartum followed by concurrent vitamin A supplementation with DPT/poliomyelitis immunization found a marginally beneficial effect on vitamin A status up to 6 months of age but not at 9 months of age (WHO/CHD Immunisation-Linked Vitamin A Supplementation Study Group 1998).

Conclusion

Evidence exists to show that a high dose of vitamin A given postpartum is beneficial to both the mother and the infant, especially among mothers with impaired vitamin A status. WHO (1998b) recently reviewed this subject and recommends a high-dose vitamin A supplement during the safe period of postpartum infertility (first 28 days in non-breast-feeding mothers and first 60 days in breast-feeding mothers) as a safe and effective intervention in vitamin A deficient areas. Vitamin A supplementation programs in developing countries need to actively consider this approach for preventing the adverse effects of vitamin A deficiency in newborns and infants under 6 months of age and for improving the vitamin A status of the mother.

9. VITAMIN A INTERACTIONS WITH IRON AND ZINC

Vitamin A deficiency is often seen with deficiencies of both energy and other micronutrients. Because iron and zinc deficiencies are so widespread and often coexist with vitamin A deficiency, their interaction with vitamin A in alleviating micronutrient deficiency status is of particular interest to public health.

Vitamin A Interaction with Iron

The interdependence of vitamin A and iron was first reported in animals by Findlay and MacKenzie in 1922 (Bloem 1995). Several animal and human studies have since confirmed these findings and offer theories about the underlying mechanism(s). These are discussed in detail in recent reviews by Lynch (1997), Bloem (1995), and Mejia (1992). Schultink and Gross (1998) also identified the possible consequences for micronutrient deficiency programs. The following is a brief summary of recent animal and human studies that have looked at the interrelationships between vitamin A and iron (Annex Table 7).

Animal Experiments

Since Findlay and MacKenzie's study in 1922, several animal experiments have reported an interaction between vitamin A and iron status. Vitamin A deficiency is known to result in mild anemia and serum retinol levels have been positively correlated with the biochemical indices of iron status, including hemoglobin and hematocrit (Roodenburg et al. 1994, Van Houwelingen et al. 1993, Sijtsma et al. 1993, Beynen et al. 1992, Mejia et al. 1979). An increase in apparent iron absorption (Roodenburg et al. 1994, Sijtsma et al. 1993) and accumulation of iron stores in the liver (Sijtsma et al. 1993, Beynen et al. 1992) and spleen (Roodenburg et al. 1994) have been observed in vitamin A deficient rats. Conversely, animals fed diets high in vitamin A have lowered liver iron stores, even when dietary iron intakes are high (Staab et al. 1984). These results suggest an impairment of the mobilization of liver iron in vitamin A deficiency.

In a recent study, Roodenburg et al. (1996) found that combined vitamin A and iron supplementation was more effective than iron supplementation alone in improving iron status in vitamin A deficient rats. Supplemental vitamin A may have contributed to erythropoiesis and iron mobilization in animals with impaired vitamin A status.

Severe vitamin A deficiency also decreases extracellular water and produces an imbalance in water regulation, leading to hemoconcentration, which may be misinterpreted as polycythemia (Bloem 1995). Thus, dehydration occurring in severe vitamin A deficiency in rats may mask the role of anemia in vitamin A deficiency (Mejia et al. 1979).

The findings of animal experiments, therefore, suggest that vitamin A deficiency causes mild anemia. An increase in iron absorption is accompanied by impaired release of iron from the liver, resulting in accumulation of iron stores in the liver and spleen. In severe vitamin A deficiency, however, an imbalance in water regulation produces dehydration that can result in hemoconcentration and, consequently, an increase in blood hemoglobin levels.

Cross-Sectional Surveys

Several observational studies have confirmed the interaction between vitamin A deficiency and iron status seen in animal experiments. A strong positive correlation existed between indices of vitamin A status (serum retinol and RBP) and indices of iron status (blood hemoglobin, hematocrit, packed cell volume, red blood cell count, and transferrin saturation) (Wolde-Gebriel et al. 1993, Suharno et al. 1992, Bloem et al. 1989, Hodges et al. 1978, Mejia et al. 1977, Mohanram et al. 1977). These correlations have been reported in various parts of the world, including Ethiopia (Wolde-Gebriel et al. 1993), Indonesia (Suharno et al. 1992), northeastern Thailand (Bloem et al. 1989), and Guatemala (Mejia et al. 1977). The population groups included pre-school children, schoolchildren, pregnant women,

and adults. Wolde-Gebriel et al. (1993) observed that the positive association between iron status and serum retinol was at least as strong as the association between serum ferritin and blood hemoglobin or transferrin saturation. Indeed, if vitamin A deficiency persisted, no improvement in mild anemia symptoms was observed with supplemental iron (Hodges et al. 1978).

Controlled Intervention Studies

Several intervention studies (Annex Table 7) looked at the effect of vitamin A supplementation, either alone or with iron, on improving vitamin A and iron status in humans. In a randomized trial in Indonesia, Suharno et al. (1993) found that administering vitamin A and iron together for 8 weeks was more effective than either nutrient alone in improving iron status in anemic pregnant women. Similarly, Mejia and Chew (1988) reported that treatment of anemic children with vitamin A and iron together resulted in a better response of serum iron and percent transferrin saturation than either vitamin A or iron treatment alone. In another study, multinutrients (iron, folate, vitamin A, and vitamin C) improved the iron status of adolescents to a greater extent than iron-folate supplements alone (Katelhut et al. 1996). Angeles-Agdeppa et al. (1997) also reported that weekly supplementation with iron and vitamin A for 3 months improved the iron status of adolescents and the benefits were sustained for about 9 months after supplementation. In India, Panth et al. (1990) found that treatment with vitamin A along with iron prevented the decline in hemoglobin that occurs at 26 to 28 weeks of gestation.

Intervention trials involving treatment with vitamin A alone also confirm the findings of the observational studies, suggesting a causal relationship between vitamin A deficiency and anemia. In Indonesian schoolchildren, a single dose of 200,000 IU of vitamin A increased serum retinol, RBP, hemoglobin, hematocrit, serum iron, and percent transferrin saturation 2 weeks after supplementation. However, no change was seen in serum ferritin concentrations (Bloem et al. 1990b). Supplementation with vitamin A capsules was shown to improve vitamin A and iron status in children in northeastern

Thailand (Bloem et al. 1989). Mohanram et al. (1977) reported that supplementation with 8 mg of retinol for 2 to 3 weeks improved hemoglobin, hematocrit, and serum iron levels in Indian children. Lower levels of hemoglobin and hematocrit were observed in vitamin A deficient children than in children with adequate vitamin A status (Mohanram et al. 1977).

The strong association between vitamin A and iron status is also evident from a fortification study. Mejia and Arroyave's (1982) longitudinal evaluation of the Guatemalan national vitamin A sugar fortification program on preschoolers found a positive correlation between changes in vitamin A status and iron status 6 months after fortification began. A significant improvement in vitamin A status was observed 1 year after the program began and the beneficial effect of fortification on indices of vitamin A and iron status were apparent 2 years after start-up (Mejia and Arroyave 1982, Arroyave et al. 1981). Muhilal et al. (1988a, 1988b) evaluated the vitamin A and iron status of adults and children in five villages in Indonesia who received monosodium glutamate (MSG) fortified with 810 µg of retinol equivalent (RE) per g of MSG. Compared with inhabitants of villages not receiving fortified MSG, hemoglobin levels and linear growth rates improved and the prevalence of Bitot's spots and overall mortality decreased among children in the intervention villages. Similarly, serum and breast milk vitamin A levels increased among lactating women in villages receiving the vitamin A fortified MSG. A recent study by Layrisse et al. (1997) found that vitamin A added to precooked maize flour diminished the inhibitory effects of coffee or tea on iron absorption from maize bread. The authors postulated this may be due to vitamin A forming a soluble complex with iron within the digestive tract, thus enhancing iron absorption. Although this study presented a plausible and interesting hypothesis, the interpretation of results was not fully supported by the data³; thus, the conclusion is questionable.

An important factor that needs to be considered in reviewing the association between vitamin A and iron is the role of infection. Infections are highly prevalent in many areas where vitamin A and iron

³ For example, the cereal phytate to iron ratios were not reported; baseline iron status differed between the groups; and methodological details related to storage, baking and analytical procedures, all of which could have affected the results, were not stated.

deficiencies are common. Recently, Northrop-Clewes et al. (1996) found that supplementation with iron for 3 months increased levels of hemoglobin and ferritin as well as the acute-phase protein antichymotrypsin (ACT) among 2-year-old children in Pakistan. This finding supports the hypothesis that iron treatment may increase the severity of infections (Ribaya-Mercado 1997). A protective role for vitamin A was also evident in the same study, where increased serum retinol levels were associated with a decrease in ACT and other markers of infection, including IgA and IgM. The latter suggests an anti-infective role for vitamin A against the potentially toxic effects of iron supplementation.

Conclusion

Although a strong interrelationship exists between vitamin A status and iron metabolism in populations where both vitamin A and iron deficiency are prevalent, the mechanism(s) of the interaction remains to be explained. In addition, how severe the deficiencies must be to show an interaction or to elicit a response to supplementation is unknown. It is speculated that, in vitamin A deficiency, iron absorption is increased and iron mobilization is impaired. Synthesis of the iron transport protein transferrin also may be impaired (Mejia and Arroyave 1982). Vitamin A deficiency may exert its effects on iron status by inhibiting the reutilization of iron for erythropoiesis (Bloem 1995). Whatever the mechanism, vitamin A plays an important role in improving iron status, and supplementation with both vitamin A and iron offers benefits in addition to those with iron alone.

Vitamin A Interaction with Zinc

The interrelationship between vitamin A and zinc is receiving increasing attention, as its relevance to public health becomes more apparent; this was reviewed earlier by Smith (1982).

Animal Experiments

Many animal experiments conducted in the 1970s consistently showed that zinc deficiency adversely affects vitamin A status. The lowered plasma retinol,

however, was a result not of zinc deficiency per se but of a decrease in food intakes observed in zinc deficiency (Smith 1982). Serum RBP levels are also lowered in zinc-deficient animals, possibly because of impaired RBP synthesis (Smith 1982). On the other hand, vitamin A deficiency has been reported to decrease zinc concentrations in the heart but only when dietary copper was also restricted (Van Houwelingen et al. 1993).

Human Studies

Observational studies have reported an association between zinc deficiency and vitamin A status (Ahmed et al. 1993b, Coutsoydis et al. 1991b, Udomkesmalee et al. 1990, Smith 1982) (Annex Table 7) and limited controlled intervention trials suggest that zinc supplementation may be beneficial in alleviating symptoms of vitamin A deficiency. Udomkesmalee et al. (1992) reported that supplementation with zinc alone improved vision, but not serum retinol or RBP levels, among children with marginal vitamin A and zinc status. Supplementation with both zinc and vitamin A normalized conjunctival epithelium, as measured by conjunctival impression cytology, but did not improve vision. Another study found that supplemental zinc alone improved vitamin A status among children with protein-energy malnutrition but not among vitamin A deficient children (Shingwekar et al. 1979); thus, zinc status must be sufficiently deficient for there to be a vitamin A response to zinc supplementation.

Conclusion

Although it is known that interactions between vitamin A and zinc exist, very little is known about the mechanism(s), the level of interaction, or the effect of zinc supplementation on vitamin A deficiency. Further studies are needed before programmatic implications can be drawn.

10. β -CAROTENE AS A SOURCE OF VITAMIN A AND ITS ROLE IN PREVENTION AND CONTROL OF VITAMIN A DEFICIENCY

This chapter reviews the human studies on purified β -carotene supplements and/or consumption of fruits and vegetables that have been conducted to determine whether β -carotene can alter the vitamin A status of deficient populations.

β -Carotene is the primary provitamin A in fruits and vegetables and is found naturally as the all-*trans* isomer. The *cis* isomers, which exist naturally and are formed during food preparation, have lower biological activity (Rodriguez-Amaya 1993). Provitamin A carotenoids account for between 60% and 90% of vitamin A intake; dependence on them as a source of vitamin A is particularly high in southeast Asia, Africa, and the western Pacific (WHO 1995).

Many studies have been conducted to assess the bioconversion of β -carotene to vitamin A in animals. More recently, bioconversion studies with stable isotopically labeled β -carotene have been carried out to assess bioconversion in humans but the results are not yet published. The efficiency of the bioconversion of β -carotene to provitamin A has been accepted to be 6:1. This value can vary depending on vitamin A status (lower status, more efficient conversion) and amount of β -carotene consumed (more consumed, less efficient conversion).

Intervention Studies

Several human studies involving β -carotene supplementation and/or consumption of fruits and vegetables have been conducted to find out whether β -carotene can alter vitamin A status, particularly in a vitamin A deficient population. All but two of these studies were conducted among children in countries where vitamin A deficiency is prevalent and have been comprehensively reviewed by de Pee and West (1996).

Of the 20 studies (Annex Table 8) carried out in children, 18 showed an improvement in vitamin A

status after consumption of either purified β -carotene or β -carotene-rich foods. Of these, 13 showed an improvement in vitamin A status after consumption of 0.8 to 19 mg of β -carotene as β -carotene-rich fruits and vegetables; 4 showed an improvement in vitamin A status after consumption of 1.8 to 7.8 mg of β -carotene as red palm oil; and 3 showed an improvement in vitamin A status after consumption of 1.2 to 2.4 mg of β -carotene as purified β -carotene. The 2 studies that showed no effect on vitamin A status (Bulux et al. 1994, Hussein and El Tohamy 1990) were conducted among children who did not have overall vitamin A deficiency.

The efficacy of β -carotene compared with vitamin A in improving vitamin A status was investigated in a few studies. Supplementing children with 0.8 to 7.8 mg of β -carotene as red palm oil had a benefit similar to that of vitamin A (Manorama et al. 1996, Rukmini 1994, Lian et al. 1967, Roels et al. 1963). Hussein and El-Tohamy (1989) reported that β -carotene-rich foods (2.4 to 3.7 mg of β -carotene) had an effect similar to a megadose of vitamin A supplement in improving vitamin A status, and Carlier et al.'s (1993) study in Senegal showed that purified β -carotene and vitamin A supplements similarly reduced the prevalence of abnormal eye cytology. Devadas et al.'s (1978) study in India, which included vitamin A deficient children, showed that β -carotene-rich foods and purified β -carotene improved vitamin A status to the same extent. A later study by Devadas et al. (1980) in India showed that both β -carotene-rich foods and vitamin A improved vitamin A status, but the improvement was greater with vitamin A than with β -carotene-rich foods.

de Pee et al. (1998) quantified the effectiveness of dietary retinol sources (3.3 mg of β -carotene), orange-colored fruit (3.0 mg of β -carotene), and dark green leafy vegetables (4.1 mg of β -carotene) in improving vitamin A status among children with

marginal vitamin A status. Serum retinol levels increased significantly in all three treatment groups, and the difference was greater among the retinol-rich foods and fruit groups ($p < 0.001$) than in the vegetable group ($p < 0.01$) compared with the control group. The findings led the authors to propose that 1 RE is equivalent to 12 μg of β -carotene for fruit and 26 μg for leafy vegetables and carrots rather than the conventional conversion factor of 6 μg .

One of the two published studies on women showed that vitamin A status improved after 12 weeks of supplementation with 3.5 mg of purified β -carotene but not with the same amount provided through β -carotene-rich vegetables (de Pee et al. 1995). The other study showed that the incidence of night blindness in women was reduced by 38% with a weekly dose of 7000 RE of vitamin A and by 16% with an equivalent amount of purified β -carotene (Christian et al. 1998).

Limitations

Few of the intervention studies listed in Annex Table 8 were adequately controlled. Among the 20 studies in children, only 6 had both negative and positive controls (de Pee et al. 1998, Bulux et al. 1994, Devadas et al. 1980, Lian et al. 1967, Roels et al. 1963, Roels et al. 1958). Four other studies had positive controls only (Manorama et al. 1996, Rukmini 1994, Carlier et al. 1993, Hussein and El-Tohamy 1989), 2 had negative controls only (Wadhwa et al. 1994, Jalal et al. 1998), and the remaining 8 had either inadequate or no controls (Hussein and El-Tohamy 1990, Mariath et al. 1989, Charoenkiatkul et al. 1985, Jayarajan et al. 1980, Devadas et al. 1978, Devadas and Murthy 1978, Lala and Reddy 1970, Pereira and Begum 1968).

Other weaknesses in the experimental designs of these intervention studies include the following:

- Fat is important for provitamin A absorption and a minimum of 5 g of oil is generally accepted as being needed for β -carotene absorp-

tion. However, Wadhwa et al. (1994), Hussein and El-Tohamy (1990), Devadas et al. (1980), Devadas et al. (1978), Devadas and Murthy (1978), and Pereira and Begum (1968) did not provide information on the fat content of the intervention and Mariath et al. (1989) did not provide information on the fat content in the daily diet.

- Routine vitamin supplements were consumed by subjects until the outset of the study (Charoenkiatkul et al. 1985); thus, the baseline retinol levels were variable.
- The sample either was too small, not randomized, or reflected a large dropout in the number of participants in the studies by Hussein and El-Tohamy (1989), Devadas et al. (1980), Devadas et al. (1978), Lala and Reddy (1970), and Roels et al. (1958).
- Wadhwa et al. (1994) did not measure vitamin A status at the baseline, and the children in the Bulux et al. (1994) study did not have overall vitamin A deficiency at the baseline.

Conclusion

Based on the evidence to date, there is clearly a dearth of data from well-designed studies to argue that, except for red palm oil, β -carotene-rich foods are effective for eliminating vitamin A deficiency. Nevertheless, the data do show that β -carotene-rich foods are important for preventing vitamin A deficiency. New data show that orange-colored fruits may be better sources of bioavailable vitamin A than dark green leafy vegetables or carrots, which is likely to be related to the food matrix. Although the conversion factor of 6 μg of β -carotene to 1 RE has been generally accepted, there is now debate on not only whether this needs to be revised but also whether specific conversion factors are needed for different foods, such as tubers, orange-colored fruits, yellow-colored fruits, leafy vegetables, and so forth.

11. SUMMARY, PROGRAM IMPLICATIONS, AND FUTURE DIRECTIONS

This chapter starts by identifying the limitations of the review before summarizing the program implications identified in the review. It then goes on to state research efforts that are currently under way and the research gaps that need to be filled to make intervention programs more effective. The focus for the future is on applied and operations research rather than basic research.

Limitations of the Review

As described in Chapter 2, this review includes only studies published in English in peer-reviewed journals that are available on the Medline database. Research that was recently completed is included. Because the scope of this review was limited to published research, other important findings of relevance that have not been published in peer-reviewed journals may exist—for example, programmatic and field experiences on the effectiveness of programs.

Most of the studies published in recent years have been included in this review. Among those published before 1980, only key studies of particular relevance to the subject were chosen for tabulation. Thus, this review is not a comprehensive compilation of all published studies available on the subject.

Program Implications

Vitamin A plays a key role in developing an immune response to infection. Consequently, vitamin A deficiency is commonly observed in the presence of infections and has been strongly associated with morbidity and mortality due to infections, especially in infancy and childhood.

Investigations on the effect of vitamin A therapy have shown unequivocal results for reducing measles-related pneumonia but no effect on other pneumonia. Studies that have looked at the effect of vitamin A supplementation in reducing morbidity symptoms, however, have provided equivocal results. There is

some evidence that, by improving vitamin A status, supplementation may decrease the severity of and complications from measles and diarrhea, although it has no effect on the prevalence or incidence of diarrhea itself. Because diarrhea and measles are two important causes of child mortality, the IVACG recommends including vitamin A supplements in all child survival programs where vitamin A deficiency is endemic. The effects of vitamin A supplementation in respiratory disease or parasitic and malarial infections are not yet clear. Future investigations will help identify the effect of vitamin A supplementation in reducing morbidity and mortality associated with these infections.

With respect to the role of vitamin A in HIV infection, human observational studies suggest that vitamin A has a protective role. However, these findings have not been substantiated through controlled intervention trials. Vitamin A supplementation studies provide conflicting data on the role of vitamin A in enhancing immunity, controlling viral load, and promoting the health of mother and infant in the presence of HIV infection. A reliable indicator of vitamin A status in the presence of infection is also lacking. Given the magnitude and rapid spread of HIV disease, these questions need to be actively researched, the effect of vitamin A supplementation needs to be established, and both policy and program recommendations need to be considered.

Interest is growing to include vitamin A supplements as part of the regular immunization program to increase the coverage of vitamin A supplementation in infants. Studies show that administering 100,000 IU of vitamin A along with measles vaccine at 6 months of age, or at both 6 and 9 months of age, does not interfere with the efficacy of measles vaccine and is safe. Concurrent doses of 25,000 IU of vitamin A with DPT/polio-myelitis immunization at 6, 10, and 14 weeks, following a postpartum megadose of vitamin A supplementation to the mother, improved both vitamin A status and morbidity but only up to 6 months of age.

Human observational and intervention studies have shown that maternal vitamin A supplementation of up to 8000 IU/day before and during pregnancy is safe. Daily doses above 10,000 IU of vitamin A during pregnancy, especially early pregnancy, may cause major birth defects. Vitamin A supplementation programs for pregnant women need to follow these guidelines set forth by the Teratology Society and the Centers for Disease Control.

No evidence exists to show a morbidity or mortality benefit from vitamin A supplementation among infants less than 5 months old. Among lactating women, however, considerable evidence is available to suggest that a high dose of vitamin A given postpartum is beneficial to both the mother and infant, especially in mothers with impaired vitamin A status. Vitamin A supplementation programs in developing countries need to seriously consider this intervention for preventing the adverse effects of vitamin A deficiency in infants and improving the vitamin A status of the mother.

Considering that deficiencies of vitamin A, iron, and zinc commonly occur together, exploring the potential benefits of multimicronutrient supplements is important. Scientific evidence suggests that vitamin A plays an important role in improving iron status among the iron deficient, and supplementation with vitamin A and iron may be more effective than iron supplementation alone. Iron supplementation programs for the prevention and treatment of anemia should consider including vitamin A supplements in their regimens. An interaction between vitamin A and zinc also exists, but the effect of zinc supplementation on vitamin A deficiency is not yet known. Further studies are needed before programmatic implications can be drawn.

The technology to prevent and treat vitamin A deficiency exists, be it through high-dose vitamin A supplements, fortification of food with vitamin A, or increased intakes of vitamin A rich foods. Yet, vitamin A deficiency is still a major public health problem in developing countries. This suggests that the effectiveness of vitamin A programs remains elusive for both physiological effect and changing perceptions, attitudes, and behavior toward vitamin A interventions from the level of policy makers to households. As science gets translated into programs, it is important to give as much attention to monitoring the

effectiveness of programs as it is to monitoring the efficacy of the trials because, as Schultink and Gross (1998) point out, the effects observed in small-scale field trials may not be the same for large-scale programs.

Factors that limit the effectiveness of programs include a lack of resources, improper training of personnel, cultural factors that may affect the acceptability of the programs, logistical problems, and a lack of interest or commitment by the public and private sectors, all of which determine whether a program is sustainable.

Current Research

Before describing the research gaps, it is important to highlight the major research efforts currently under way. Ongoing vitamin A research can be categorized as assessment, maternal and child health and survival, infection, and improving vitamin A status through dietary sources.

Assessment

Activities under way include assessment of vitamin A status with the following:

- High-pressure liquid chromatography (HPLC) analysis for serum retinol from dried blood spots,
- Holo-RBP analysis in microvolumes of serum and dried whole blood,
- A rapid enzyme immunoassay microwell strip test for measuring RBP,
- HPLC versus enzyme-linked immunosorbent assay versus spectrophotometry versus fluorimetry for retinol in serum/plasma,
- A retinoyl β -glucuronide hydrolysis test,
- The refined modified relative dose response,
- The RBP/transthyretin ratio, and
- A portable dark adaptometer to measure night blindness in women.

Besides identifying status, retinol levels reflect increased excretion and/or mobilization of vitamin A. Limited research is ongoing to

- Determine urinary losses of vitamin A during different types of morbidity in different environments, its effect on daily requirements, and

the effect of vitamin A supplements on urinary vitamin A losses;

- Develop assessment methods to find out whether an individual's reduced serum retinol is a result of an acute-phase response and/or poor vitamin A status and develop adjustment factors, if necessary; and
- Study the metabolism and biokinetics of vitamin A by using stable isotopes.

Maternal and Child Health and Survival

A study on the efficacy of low-dose vitamin A and purified β -carotene supplementation on maternal mortality, pregnancy outcome, and vitamin A status of infants was recently completed in Nepal and reports are in preparation.

Other work in progress includes the following:

- Determining the effects of vitamin A supplementation to mothers and/or infants with Expanded Program of Immunization (EPI) on antibody response;
- Identifying the mortality and growth effects of concurrent vitamin A supplementation and deworming with albendazole;
- Investigating the therapeutic potential of a high-dose vitamin A supplement for preschool children in relation to survival, complications, and recovery during hospitalization with severe malaria.

Infection

Studies have been recently completed in Malawi and Tanzania and are under way in South Africa, Zimbabwe, and Uganda on HIV issues including the following:

- Micronutrient status and HIV transmission,
- The effect of vitamin A supplementation on maternal-infant HIV transmission during pregnancy and lactation,
- The use of vitamin A as therapy for reducing the progression of HIV and improving the survival of HIV-infected preschool children, and
- The effect of prenatal vitamin A supplementation on immune factors in breast milk of HIV-infected mothers.

Other important associations between vitamin A and communicable diseases that are being studied include the effect of the following:

- Vitamin A supplementation on immune responsiveness among children with malaria,
- Weekly low-dose vitamin A supplementation on the gut integrity of infants,
- Vitamin A supplementation of infants with respiratory infections,
- Combined vitamin A and zinc therapy on the duration and severity of diarrheal disease, and
- Recurrent infection on vitamin A stores in children recently supplemented with a high dose of vitamin A.

Dietary Improvement

Although β -carotene is an important source of dietary vitamin A, its bioavailability may be limited by both the food matrix and host-related factors, which is likely the reason for the relatively poor performance of diet-based interventions. Research is under way to:

- Develop methods to measure carotenoid bioavailability and bioconversion to retinol by using isotopically labeled carotenoid and retinol;
- Determine whether foods rich in provitamin A carotenoids improve status in malnourished children and pregnant/lactating women;
- Clarify the contributions of dietary carotenoids to human vitamin A requirements and understand how dietary modification, food matrix, and other factors affect the utilization of carotenoids; and
- Assess the effect of simultaneous zinc and vitamin A supplementation on vitamin A bioavailability.

Because children under 2 years old are the most vulnerable to vitamin A and other micronutrient deficiencies, improving their access to vitamin A by using micronutrient sprinkles containing vitamin A, iron, and zinc, which is added to the food just before feeding, is being tested for both efficacy and effectiveness in a multicenter trial.

Future Directions

Data are available to suggest that vitamin A may be important for maternal survival but the mechanism remains unknown. Future studies need to find out whether the effect of increased intakes of vitamin A and provitamin A carotenoids for reducing the risk of maternal and infant morbidity and mortality is periconceptual or prenatal, and the effect of the increased intake of vitamin A and β -carotene needs to be estimated. Once the biological basis is better understood, the feasibility and effectiveness of promoting the use of micronutrient supplements through Information, Education and Communication (IEC)/social marketing in family planning and other reproductive health activities should be determined.

With the reemergence of communicable diseases such as tuberculosis and the increased recognition being given to the nutritional implications of parasitic infections, the effect of vitamin A supplementation on resistance to infection and enhanced immunity, focusing on malaria, tuberculosis, diarrheal diseases, and respiratory infections needs to be clarified.

Increasingly more attention is being given to addressing the welfare of adolescent girls to optimize their nutrition and health status before they enter pregnancy and motherhood. From the vitamin A perspective, the periodicity of supplementing adolescent girls with vitamin A and/or iron/folate to prevent deficiency before and during pregnancy should be determined. Similarly, the cost-effectiveness of combinations of micronutrient supplementation with vitamin A, including with iron and folate and/or vitamin C (and/or zinc), on the micronutrient status and growth of adolescent girls before

pregnancy and on pregnancy outcomes has to be ascertained. In addition, systems for delivering micronutrient supplements to adolescent girls—e.g., schools, formal workplaces (e.g., factories), and possibly places of worship—need to be developed and tested.

Because as much as 70% of dietary vitamin A comes from β -carotene-rich fruits and vegetables, research is needed on determining the extent of the bioconversion of β -carotene to vitamin A and on identifying foods that yield the greatest bioconversion of β -carotene.

Although the efficacy of vitamin A supplementation on child survival is well documented, no data are available to show that programs are effective in improving child survival, largely because health management/information systems are weak. Strategies and tools are needed to improve the tracking and reporting of maternal, infant, and under 5 mortality to monitor the effect of service delivery at the program level.

Invariably vitamin A programs depend on behavioral change, be it that of the mother/parents and/or the health care provider delivering the intervention. There is little understanding, however, of how much behavioral change takes place and what motivates this change. To understand the latter it will be important to discern mothers' expectations about functional outcomes from their child(ren) taking vitamin A supplements or micronutrient-rich foods and whether these outcomes are measurable and can be used as indicators for improved vitamin A nutrition. Once appropriate and relevant indicators have been developed, a simple program-based quality assurance system for both micronutrient training and IEC activities can be developed.

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Annex 1. SUMMARY OF TABLES

Table 1 Effect of Vitamin A on Morbidity

Table 2 Effect of Vitamin A on Immunity

Table 3 Role of Vitamin A in HIV/AIDS Disease

Table 4 Effect of Vitamin A on the Efficacy of Vaccines

Table 5 Effect of Vitamin A During Pregnancy

Table 6 Effect of Vitamin A During Lactation

Table 7 Interaction of Vitamin A with Iron and/or Zinc

Table 8 β -Carotene As a Source of Vitamin A

Acronyms and Abbreviations Used in Tables

AGP	α -1 acid glycoprotein	Mo	month(s)
ALRI	acute lower respiratory illness	OR	odds ratio
ARI	acute respiratory illness	PCV	packed cell volume
BMI	body mass index	PEM	protein energy malnutrition
BW	body weight	RBC	red blood cell
CDC	Centers for Disease Control	RR	relative risk
CIC	conjunctival impression cytology	RSV	respiratory syncytial virus
CNS	central nervous system	suppl	supplementation
cont	control(s)	TS	transferrin saturation
DGLV	dark green leafy vegetables	TT	tetanus toxoid
Exp	experimental	VAD	vitamin A deficiency
GLV	green leafy vegetables	vit	vitamin
IL	interleukin	w/o	without
KLH	keyhole limpet hemocyanin	w/	with
MCHC	mean corpuscular hemoglobin concentration		

Table 1. Effect of Vitamin A on Morbidity

Study	Intervention	Sample	Key findings on effect on morbidity
Case-control and cohort studies			
Mitra et al. 1998b	8-mo, prospective study in Bangladesh	n = 90; 5 to 59 mo old; 66 children w/ shigellosis	<ul style="list-style-type: none"> ■ Serum retinol was lower (by 0.8 µmol/L) in children w/ <i>S. dysenteriae</i> type 1 infection than in children w/ other less virulent strains of <i>S. dysenteriae</i>. ■ Low serum retinol was independently associated w/ high fever and low weight-for-age.
Mitra et al. 1998a	8-mo, prospective study in Bangladesh	n = 66; 5 to 59 mo old; children w/ shigellosis	<ul style="list-style-type: none"> ■ Urinary retinol excretion occurred in 59% of the children w/ 8% of them excreting more than 0.1 µmol/day. ■ Impaired tubular reabsorption of proteins, such as RBP, may have caused loss of retinol in urine.
Hanekom et al. 1997	Cross-sectional survey in South Africa	Children w/ pulmonary tuberculosis	<ul style="list-style-type: none"> ■ Mean plasma vit A was 18.1 µg/dL (62% below normal) in children w/ pulmonary tuberculosis. ■ More extensive or severe disease (for example additional extrapulmonary tuberculosis) was associated w/ low plasma vit A levels. ■ High-dose vit A therapy did not affect the outcome of disease.
Semba et al. 1996	Prospective study of children hospitalized for meningococcal meningitis in Rwanda	n = 41; mean age 43 mo	<ul style="list-style-type: none"> ■ 73% of children had serum vit A levels consistent w/ subclinical deficiency (<0.7 µmol/L) and 27% had levels consistent w/ severe deficiency (<0.35 µmol/L). ■ Bacterial meningitis was characterized by VAD.
Friis et al. 1996	Cross-sectional study in Zimbabwean schoolchildren	n = 313; 11 to 17 y old	<ul style="list-style-type: none"> ■ Every 100 eggs/g increase in egg output of <i>S. mansoni</i> decreased serum retinol by 0.03 µmol/L. High intensities of <i>S. mansoni</i> infection may induce VAD. ■ <i>S. haematobium</i> did not have an effect on serum retinol.
Alvarez et al. 1995	Case-control study	n = 44 children w/ acute diarrhea, n = 44 healthy cont; 6 to 36 mo old	<ul style="list-style-type: none"> ■ Mean urinary excretion was higher in children w/ diarrhea (1.42 µmol/24 h) than cont (no measurable quantities of urinary retinol). ■ Serum retinol was negatively associated w/ duration of diarrhea before hospitalization.
Fawzi et al. 1995	Prospective study in Sudan	n = 28,753; 6 to 72 mo old	<ul style="list-style-type: none"> ■ Total dietary vit A intake was strongly and inversely associated w/ risk of diarrhea (multivariate risk 0.58) and risk of cough and fever (multivariate risk 0.60). ■ Vit A intake was also negatively associated w/ the risk of measles.
Salazar-Lindo et al. 1993	Cross-sectional study in Lima, Peru	n = 137 (72 w/ diarrhea, 65 healthy cont); 6 to 18 mo old	<ul style="list-style-type: none"> ■ Serum retinol was significantly lower in children w/ diarrhea than in those w/o diarrhea (0.51 vs. 1.00 µmol/L, p < 0.001); findings suggest that diarrhea may lead to lower circulating retinol levels.
Filteau et al. 1993	Cross-sectional, community-based study in northern Ghana	6 to 59 mo old	<ul style="list-style-type: none"> ■ Serum retinol was not associated w/ illness symptoms, but was negatively correlated w/ serum acute-phase proteins, AGP, and Serum amyloid-A ■ Malaria parasite density was negatively correlated w/serum retinol.

Table 1. Effect of Vitamin A on Morbidity (cont.)

Study	Intervention	Sample	Key findings on effect on morbidity
Case-control and cohort studies			
Tabone et al. 1992	Observational study	Patients w/ acute <i>Plasmodium falciparum</i> malaria	<ul style="list-style-type: none"> ■ IL-6 levels in serum were found to increase and decrease corresponding to parasitemia patterns. ■ Serum IL-6 was inversely related to serum vit A or its binding proteins. ■ Vit A suppl alone may not be sufficient to restore malaria-induced VAD.
Bloem et al. 1990a	Cross-sectional study in Thailand	n = 1772; 1 to 8 y old	<ul style="list-style-type: none"> ■ Children w/ a history of diarrhea or respiratory disease had lower serum retinol and RBP levels. ■ In a subset analysis of 146 children, a follow-up of 3 mo showed that VAD (serum retinol < 0.35 μmol/L) increased the risk of respiratory disease 4-fold.
Galan et al. 1990	Observational study in Congo	n = 454; preschool children	<ul style="list-style-type: none"> ■ During malarial attacks, deficient or marginal vit A status was seen in 37.5% of the children (serum retinol < 10 μg/dL). ■ Plasma retinol was lower in patients during malarial attacks than in cont (14.8 vs. 31.5 μg/dL, p < 0.001).
Shahid et al. 1988	Retrospective analysis, 2-y follow-up	n = 4155 cohort; n = 410 children w/ persistent diarrhea	<ul style="list-style-type: none"> ■ VAD and lower respiratory tract infection were independently correlated w/ persistent diarrhea.
Sturchler et al. 1987	Longitudinal study in Tanzania, 1982–1984	n = 170	<ul style="list-style-type: none"> ■ Serum retinol levels were inversely correlated w/ malaria parasitemia in 1982 and directly correlated w/ antibody titers to synthetic sporozoite peptide in 1984. ■ These correlations may have been confounded by age.
Reddy et al. 1986a	Prospective study in Indian children	n = 1544; <59 mo old	<ul style="list-style-type: none"> ■ 318 cases of measles were identified over a 15-mo study period; maximum incidence was observed in children 1 to 2 y old (105 of 318). ■ Serum vit A and RBP levels were significantly lower during the acute stage of measles (p < 0.001) but were restored to normal 8 wk after recovery.
Sommer et al. 1983	Prospective, longitudinal study of 18 mo; examined every 3 mo; conducted in Indonesia	n = 3481; 12 to 72 mo old	<ul style="list-style-type: none"> ■ Respiratory infections were more prevalent in children w/ xerophthalmia; the prevalence increased w/ the severity of xerophthalmia. ■ The prevalence of measles or chickenpox was similar in xerophthalmic and nonxerophthalmic children. ■ Children w/ mild xerophthalmia were 3 times more likely to report diarrhea than those w/o VAD at the beginning and end of the 3-mo interval.
Sturchler 1983	Observational study in rural Liberia	n = 121; adults	<ul style="list-style-type: none"> ■ Mean serum retinol and RBP levels in helminth-free et al. adults (n = 19) were 414 and 43 μg/mL, respectively; corresponding levels in adults w/ schistosomiasis (n = 20) were 339 and 35 μg/mL. ■ Schistosomiasis may be a risk factor of latent VAD.

Table 1. Effect of Vitamin A on Morbidity (cont.)

Study	Intervention	Sample	Key findings on effect on morbidity
Case-control and cohort studies			
Mikhail and Mansour 1982a	Observational study in Egyptian schistosomiasis patients	n = 91 males infected w/ schistosomiasis; n = 32 healthy cont	<ul style="list-style-type: none"> ■ Schistosomiasis patients had subnormal levels of plasma vit A, RBP, prealbumin, zinc, and albumin levels ($p < 0.005$). ■ A correlation was seen between plasma zinc and plasma vit A, RBP, or prealbumin levels ($p < 0.001$).
Mikhail and Mansour 1982b	Observational study	<i>S. mansoni</i> -infected patients	<ul style="list-style-type: none"> ■ Schistosomiasis patients had significantly depressed levels of plasma zinc, vit A, and carotenoids; the degree of this reduction was correlated w/ the associated complications of the disease.
Controlled intervention studies			
Fawzi et al. 1998a	Randomized, double-blind trial in Tanzania; 2 doses of up to 200,000 IU of vit A or placebo	n = 687; children w/ pneumonia	<ul style="list-style-type: none"> ■ 13 of 346 children in the vit A group died, compared w/ 8 of 341 in placebo group (relative mortality 1.63). ■ No differences in days of hospitalization, days of fever, rapid respiratory rate, or hypoxia were observed between the two groups.
Jalal et al. 1998	Randomized study; VAD Indonesian children w/ roundworm infection; 5.1 µg of β-carotene/day w/ or w/o deworming versus placebo	n = 242; 2-7 y old	<ul style="list-style-type: none"> ■ Suppl w/ β-carotene-rich snacks significantly improved vit A status, especially when snacks also contained fat. ■ Suppl w/ β-carotene-rich snacks significantly improved vit A status when children heavily infected w/ roundworm were also dewormed.
Nacul et al. 1997	Randomized, double-blind clinical trial in NE Brazil; up to 400,000 IU of vit A or placebo daily	n = 472; 6 to 59 mo old w/ pneumonia	<ul style="list-style-type: none"> ■ Both groups had similar overall duration of pneumonia and incidence of adverse outcomes. ■ Children receiving vit A were less likely to have fever by day 3 ($p = 0.008$) and 29% less likely to fail to respond to the first line antibiotic ($p = 0.054$).
Bresee et al. 1996	Multicenter, randomized trial; high-dose vit A	n = 239; 1 to 72 mo old w/ respiratory syncytial virus infection	<ul style="list-style-type: none"> ■ No differences in most clinical outcomes were seen between supplemented and cont groups. ■ Vit A supplemented children had longer hospital stays than cont (5.0 vs. 4.4 d, $p = 0.01$), especially in those >1 y old who received highest doses of vit A. ■ Serum retinol was inversely related to severity of illness.
Dollimore et al. 1997	Randomized, double-blind trial in N Ghana; up to 200,000 IU of vit A every 4 mo for 1 y	n = 25,443; 0 to 95 mo old	<ul style="list-style-type: none"> ■ Overall estimated measles incidence rate was 24.3 per 1000 child y, and acute case fatality was 15.7%. ■ Measles incidence was not significantly different in the vit A (23.6) and placebo groups (28.9 per 1000 child-y). ■ Among a subgroup of 946 measles cases, there was no difference in acute measles case fatality between the vit A and placebo groups (15.4% vs. 14.5%).

Table 1. Effect of Vitamin A on Morbidity (cont.)

Study	Intervention	Sample	Key findings on effect on morbidity
Controlled intervention studies			
Bhandari et al. 1997	Double-blind, controlled trial in India; one dose of 60 µg of vit A or placebo	n = 900; 12 to 59 mo old w/ acute diarrhea of ≤7 d	<ul style="list-style-type: none"> ■ Overall, children treated w/ vit A had a lower risk of persistent diarrhea (OR 0.30, p = 0.05) than cont but there was no effect on the mean duration of diarrhea or mean stool frequency. ■ In the subgroup of children who were not breast-fed, vit A reduced the mean diarrheal duration, number of stools passed, and episodes lasting >14 d (p = 0.002). ■ Similar benefits of vit A were not seen in breast-fed children.
Rosales et al. 1996	Randomized, double-blind, clinical trial in Zambia; 210 µmol of retinol	n = 200; 5 mo to 17 y old w/ measles	<ul style="list-style-type: none"> ■ Incidence of measles-associated cough or pneumonia in asymptomatic measles patients was lower in vit A group, but recovery from pneumonia was better in the placebo group. ■ One-dose of vit A to prevent measles complications may not be as efficacious as two doses of 200,000 IU.
Dowell et al. 1996	Randomized, placebo-controlled trial in Chile; 50,000 to 200,000 IU of vit A	n = 89 exp; n = 91 cont; 1 to 73 mo old w/ respiratory syncytial virus infection	<ul style="list-style-type: none"> ■ Overall, suppl w/ vit A did not affect duration of hospitalization, need for supplemental oxygen, or time to resolve hypoxemia. ■ In children w/ significant hypoxemia (oxygen saturation level < 90%), vit A caused a more rapid resolution of tachypnea (p = 0.01) and shorter duration of hospitalization (5.5 vs. 9.3 days, p = 0.09).
Quinlan and Hayani 1996	Observational study and a randomized controlled trial; single dose of 100,000 IU of oral vit A or placebo	n = 32 children w/ RSV infection; n = 39 healthy cont	<ul style="list-style-type: none"> ■ Mean vit A and RBP levels were lower in RSV-infected children than in healthy cont (p > 0.05). ■ Among children infected w/ RSV, vit A treatment did not affect severity score, mean days of hospitalization, intensive care, or receipt of supplemental oxygen (n = 21 exp, n = 11 placebo; p < 0.05).
Tanumihardjo et al. 1996	Randomized, controlled trial of Indonesian children w/ <i>A. lumbricoides</i> ; 200,000 IU of vit A; 400 µg of albendazole	n = 309; 0.6 to 6.6 y old	<ul style="list-style-type: none"> ■ Vit A suppl improved vit A status (p < 0.0001); deworming alone did not improve vit A status (p = 0.370). ■ Serum retinols marginally improved in two of the three groups receiving vit A along w/ albendazole (p = 0.051).
Coutsoudis et al. 1995b	Randomized, placebo-controlled trial in S Africa; up to 200,000 IU of vit A	n = 118; 1 to 15 mo old w/ HIV-infected mothers	<ul style="list-style-type: none"> ■ Among all children, overall morbidity was lower in the vit A supplemented group than in cont (OR = 0.69). ■ Among children w/ known HIV status (28 infected, 57 uninfected), diarrheal morbidity was significantly reduced in vit A suppl infected children (OR = 0.51). ■ Diarrheal morbidity was unaffected by vit A in uninfected children.
Filteau et al. 1995	Randomized, double-blind trial in N Ghana; up to 200,000 IU of vit A every 4 mo for 1 y	n = 1455; 6 to 59 mo old	<ul style="list-style-type: none"> ■ Acute-phase protein responses to fever and cough were not affected by vit A suppl. ■ Vomiting and severe diarrhea were associated w/ greater increases in acute-phase protein levels in the supplemented group compared w/ the cont group.

Table 1. Effect of Vitamin A on Morbidity (cont.)

Study	Intervention	Sample	Key findings on effect on morbidity
Controlled intervention studies			
Ross et al. 1995	Randomized, double-blind trial in N Ghana; up to 200,000 IU of vit A every 4 mo for 1 y	n = 1,455; 6 to 57 mo old	<ul style="list-style-type: none"> ■ Vit A suppl significantly reduced the overall incidence of severe diarrhea, clinic attendances, hospital admissions, and mortality. ■ The impact of each dose of vit A was not affected by the number of previous doses or the time of year. ■ Effectiveness of supplement did not wane during the 4-mo interval between doses.
Ramakrishnan et al. 1995	Randomized, double-blind trial in southern India; 200,000 IU of vit A every 4 mo for 1 y	n = 309 exp; n = 274 cont; <3 y old	<ul style="list-style-type: none"> ■ The mean numbers of episodes per child-year were 2.62 and 2.56 for respiratory illness, and 1.9 and 1.77 for diarrhea, for the supplemented and cont groups, respectively; the differences were not significant. ■ Vit A suppl did not reduce common morbidity in children w/ mild-to-moderate VAD.
Velasquez-Melendez et al. 1995	Randomized, clinical trial of children w/ pneumonia; up to 200,000 IU of vit A	n = 34; 7 mo to 8 y old	<ul style="list-style-type: none"> ■ After 1 wk of routine treatment for pneumonia, plasma retinol and RBP increased in both supplemented and cont groups; retinol levels in the two groups were not significantly different (26.5 vs. 24.1 µg/dL, p < 0.05).
Binka et al. 1995	Randomized, double-blind trial in N Ghana; up to 200,000 IU of vit A every 4 mo for 1 y	n = 1,455; 6 to 59 mo old	<ul style="list-style-type: none"> ■ There was no difference between children supplemented w/ vit A or placebo in fever incidence, malaria parasitemia rates, parasite densities, or rates of probable malarial illness (p < 0.05).
En-Lin et al. 1995	1 y randomized trial; 2 doses of 200,000 IU of vit A (given at 4 and 10 mo of follow-up)	n = 98 exp; n = 74 cont; 6 to 36 mo old	<ul style="list-style-type: none"> ■ Significant reductions (p < 0.01) in the incidence of diarrhea (0.71 vs. 1.76, ratio 2.5) and respiratory disease (0.52 vs. 1.77, ratio 3.4) were observed in supplemented children compared w/ the cont group. ■ Serum vit A was higher in the supplemented group than in the cont group 8 weeks after suppl.
Dibley et al. 1996	Individually randomized, double-blind study in Indonesia; up to 206,000 IU of vit A every 4 mo	n = 1407; 6 to 47 mo old	<ul style="list-style-type: none"> ■ Vit A suppl increased the incidence of ARI by 8% and ALRI by 39%. ■ The detrimental effect on ALRI was most pronounced in children of adequate nutritional status (RR 1.83, p < 0.05); in chronically malnourished children, vit A was protective (RR 0.71, p < 0.05). ■ Vit A suppl did not affect the overall incidence of diarrhea (RR 1.06, p < 0.05).
Barreto et al. 1994	Randomized, double-blind community trial in Brazil; up to 200,000 IU of vit A every 4 mo for 1 y	n = 1,240; 6 to 48 mo old	<ul style="list-style-type: none"> ■ Overall incidence of diarrhea episodes was significantly lower in the supplemented group than in cont (rate ratio 0.94; p < 0.05). ■ Benefit of suppl was greater w/ severity of diarrhea; incidence of severe diarrhea was 20% lower in the supplemented group (rate ratio 0.80; p < 0.05). ■ Vit A did not affect incidence of ALRI.
Rosales and Kjolhede 1994	Randomized, double-blind, clinical trial in Zambia; 210 µmol of retinol	n = 200; 5 mo to 17 y old children w/ measles	<ul style="list-style-type: none"> ■ Children in both supplemented and cont groups had significant increases in measles antibody titer from baseline to wk 2; these increments were not significantly different (p = 0.25). ■ Vit A did not reduce measles-associated morbidity.

Table 1. Effect of Vitamin A on Morbidity (cont.)

Study	Intervention	Sample	Key findings on effect on morbidity
Controlled intervention studies			
Pandey et al. 1991	Vit A suppl program, Nepal; up to 200,000 IU of vit A every 4 mo for 1 y	All children <5 y old	<ul style="list-style-type: none"> ■ The communities that received early dosing w/ vit A showed a 33% lower rate of pneumonia cases. ■ Overall mortality was reduced in supplemented children (RR 0.74; in children 6 to 11 mo, RR 0.51).
Lie et al. 1993	1 y randomized, double-blind study in China; 2 doses of 200,000 IU of vit A	n = 98 exp; n = 74 cont; 6 to 36 mo old	<ul style="list-style-type: none"> ■ The incidence of diarrhea ($p < 0.01$) and respiratory disease ($p < 0.01$) was significantly reduced in treatment group; risk of diarrhea and respiratory disease was, respectively, 2.5 and 3.4 times higher in cont. ■ The severity of diarrhea and respiratory disease was also decreased in the supplemented group.
Hussey and Klein 1993	Retrospective study of children hospitalized for measles, and treated w/ 200,000 IU (standard) or 400,000 IU (Hi-VAT)	n = 1,720; <15 y old	<ul style="list-style-type: none"> ■ Compared w/ children on standard therapy (n = 1061), children receiving Hi-VAT (n = 651) had a shorter hospital stay (10 vs. 13 days, $p < 0.001$), a lower incidence of intensive care (4.3% vs. 10.5%, $p < 0.001$), and a lower death rate (1.6% vs. 5%, $p < 0.001$). ■ No adverse effects of Hi-VAT were observed.
Stansfield et al. 1993	Double-blind, placebo-controlled study in Haiti; 200,000 IU or placebo every 4 mo	n = 11,124; 6 to 83 mo old	<ul style="list-style-type: none"> ■ The vit A treated group had an increased 2-wk prevalence of diarrhea (RR 1.09), rhinitis (RR 1.02), cold/flu symptoms (RR 1.04), cough (RR 1.07), and rapid breathing (RR 1.18) compared w/ cont.
Ahmed et al. 1993a	Intervention study in Bangladesh; 41.8 μ mol of retinol	n = 10 children w/ ascariasis; 4 to 10 y old	<ul style="list-style-type: none"> ■ Less than 1% of the retinol supplement was recovered from the stools collected over a 48-h follow-up period. ■ No retinol was detected in <i>Ascaris</i> worms in stools. ■ Ascariasis may not predispose to malabsorption of vit A.
Coutsoudis et al. 1992	Randomized, double-blind trial; 4 doses of up to 200,000 IU of vit A	n = 29 exp; n = 31 cont; 4 to 24 mo old children w/ measles	<ul style="list-style-type: none"> ■ A significant reduction was observed in morbidity in the supplemented group during the acute (day 8, $p = 0.006$) and chronic (day 42, $p = 0.02$; 6 mo, $p = 0.02$) phases.
Arthur et al. 1992	Randomized, double-blind trial in N Ghana; up to 200,000 IU of vit A every 4 mo for 1 y	n = 1455; 6 to 59 mo old	<ul style="list-style-type: none"> ■ Mean daily prevalence of 19 of 21 morbidity symptoms did not differ between the supplemented and cont groups; however, daily prevalence of vomiting was 13% lower in the supplemented group (1.91% vs. 2.19%, RR 0.87, $p = 0.02$). ■ Vit A reduced the severity of illness episodes: rate of clinic attendances was 12% lower (RR 0.88, $p < 0.002$), and rate of hospital admissions was 38% lower (RR 0.62, $p < 0.02$) in the supplemented group.
Henning et al. 1992	Randomized, clinical trial; single dose of 200,000 IU of vit A or placebo	n = 83 children hospitalized for noncholera, watery diarrhea	<ul style="list-style-type: none"> ■ No differences between groups in the duration of illness or stool output. ■ No adverse effects of high-dose vit A treatment.

Table 1. Effect of Vitamin A on Morbidity (cont.)

Study	Intervention	Sample	Key findings on effect on morbidity
Controlled intervention studies			
Coutsoudis et al. 1991a	Randomized, double-blind trial in South Africa; 3 doses of up to 109 µg of vit A	n = 60; 4 to 24 mo old children w/ complicated measles	<ul style="list-style-type: none"> ■ The severity of morbidity conditions (diarrhea, herpes, and respiratory tract infection), measured as integrated morbidity scores, was reduced by 82%, 61%, and 85% on day 8, 6 wk, and 6 mo of follow-up, respectively, in the supplemented group compared w/ cont. ■ Vit A treated children recovered more rapidly from pneumonia (3.8 vs. 5.7 d, $p < 0.05$), diarrhea, and fever than did cont; the latter two were not significantly different.
Coutsoudis et al. 1991b	Randomized, double-blind trial in South African children w/ measles; 200,000 IU of vit A	n = 29 exp; n = 31 cont; 4 to 24 mo old	<ul style="list-style-type: none"> ■ Serum retinol and RBP were significantly lower in measles patients compared w/ healthy cont. ■ Vit A and prealbumin levels on day 8 were significantly higher in the supplemented than in the placebo group. ■ Mobilization of vit A was impaired during measles.
Rahmathullah et al. 1991	Randomized, placebo-controlled, masked clinical trial in India; weekly dose of 8333 IU for 52 wk	n = 15,419; 6 to 60 mo old	<ul style="list-style-type: none"> ■ The incidence, severity, and duration of diarrhea and respiratory infections were similar in both treated and untreated groups.
Vijayaraghavan et al. 1990	2 y, prospective, double-blind, placebo-controlled study in India; 1 or 2 doses of 200,000 IU of vit A	n = 7,691 exp; n = 8084 cont; 1 to 5 y old	<ul style="list-style-type: none"> ■ The risk of respiratory infection, but not diarrhea, was higher in children w/ mild xerophthalmia. ■ Vit A suppl did not have an effect on morbidity status (diarrhea, respiratory illness).
Abdeljaber et al. 1990	Randomized, community intervention trial; 2 doses of 200,000 IU 6 mo apart	n = 229 exp; n = 221 cont; 1 to 5 y old	<ul style="list-style-type: none"> ■ The prevalence of cough, fever, and diarrhea was 17.0%, 25.0%, and 4.0% in the treatment group, and 18.6%, 26.7%, and 4.5% in the cont group. The differences between the two groups were not statistically significant ($p > 0.05$). ■ The prevalence of morbidity symptoms was significantly ($p < 0.05$) higher w/ higher levels of malnutrition (height-for-age).
Bloem et al. 1990a	Intervention trial; 200,000 IU of vit A, 2-mo follow-up period	n = 166; 1 to 5 y old	<ul style="list-style-type: none"> ■ Among children age 3 to 5 y, the cont group had a higher incidence of respiratory disease (2.9 times) and diarrhea (3.1 times) during 2 mo of follow-up. ■ Children age 1 to 2 y had a significantly higher incidence of respiratory disease (2.5 times) between 2 and 4 mo of follow-up compared w/ the older children.

Table 1. Effect of Vitamin A on Morbidity (cont.)

Study	Intervention	Sample	Key findings on effect on morbidity
Controlled intervention studies			
Pinnock et al. 1988	Randomized, controlled trial; weekly dose of 4.2 µg of retinol for 1 y	n = 206; 2- to 7-y-olds w/ bronchiolitis in infancy	<ul style="list-style-type: none"> ■ Plasma retinol was comparable in treatment and placebo groups at baseline and after 12 mo of suppl. ■ Respiratory morbidity (median days of symptoms, episodes of symptoms, scripts of antibiotics, and number of doctor visits) was similar in both groups.
Pinnock et al. 1986	Randomized, controlled trial; 1160 µg of vit A given 3 times a wk (450 µg/day); 11 mo of follow-up	n = 147; 1 to 4 y old; history of respiratory illness	<ul style="list-style-type: none"> ■ Children receiving vit A experienced 19% fewer episodes of respiratory symptomatology (p < 0.05) than cont. ■ Plasma retinol levels were similar in both groups before and after suppl.
Molla et al. 1983	Clinical trial of patients n = 13; w/ acute diarrhea; single dose 7500 IU/kg	3 to 9 y old	<ul style="list-style-type: none"> ■ Patients w/ various eye signs resulting from VAD showed clinical improvement in vision within a few days after vit A given during acute diarrhea.
Sinha et al. 1976	Study in West Bengal, India; 200,000 IU every 4 mo	0- to 4½-y-old children	<ul style="list-style-type: none"> ■ Vit A suppl did not have an effect on the diarrheal rates in this study population.
Ellison 1932	Randomized trial of children w/ measles; 300 IU of vit A daily for 1 to 3 wk	n = 600 exp; n = 300 cont; <5 y old	<ul style="list-style-type: none"> ■ Number of deaths in supplemented group was 11 compared w/ 26 in the cont group. ■ Pulmonary complications were less severe in the supplemented group than in the cont; no differences in otological or cutaneous complications were observed.
In vitro study			
Crowle and Ross 1989	Retinoic acid; exp infection w/ M. tuberculosis Erdman	Human macrophage cell cultures	<ul style="list-style-type: none"> ■ Retinoic acid was protective when added after infection at the pharmacologic concentration of 10 mM and when added before infection at the physiologic concentration of 0.01 mM; protection was strongest at concentrations of serum below 1%. ■ Results suggest an immunoprotective role for vit A against human tuberculosis.

Table 2. Effect of Vitamin A on Immunity

Study	Intervention	Sample	Key findings on effect on immunity
Case-control studies			
Semba et al. 1996	Prospective study of children hospitalized for meningococcal meningitis in Rwanda	n = 41; mean age 3.6 y	<ul style="list-style-type: none"> ■ Mean CD4 percent was higher and CD8 percent was lower in children w/ bacterial meningitis compared w/ known reference populations. ■ Children w/ a higher degree of VAD (<0.60 µmol/L) had a significantly lower CD8 percent (p = 0.03) and higher CD4/CD8 ratio (p = 0.05) than those w/ a lower degree of VAD (>0.60 µmol/L).
Semba et al. 1993a	Longitudinal study; mean follow-up of 22.8 mo	n = 179 subsample of >2000 injected drug users (IDUs)	<ul style="list-style-type: none"> ■ More than 15% of the HIV-1-seropositive subjects were vit A deficient (plasma vit A < 1.05 µmol/L); HIV-1-seropositive subjects had lower mean plasma vit A than seronegative subjects (p < 0.001). ■ VAD was associated w/ lower CD4 counts in both seropositive and seronegative subjects (p < 0.05) and increased mortality (RR 6.3) in seropositive subjects.
Controlled intervention studies			
Rahman et al. 1997	Randomized, placebo-controlled trial; 3 doses of 15 µg of vit A given at time of monthly DPT/OPV immunizations	n = 62 exp; n = 50 cont; <6 mo old	<ul style="list-style-type: none"> ■ The response to delayed cutaneous hypersensitivity test (CMI) was similar in vit A and cont groups. ■ In infants w/ adequate serum retinol (>0.7 µmol/L), after suppl, the vit A group had higher positive CMI tests than cont (p = 0.008). ■ In infants w/ low serum retinol (<0.7 µmol/L) after suppl, vit A had no effect on CMI response. ■ CMI response was consistently better in well-nourished infants, irrespective of vit A suppl (p < 0.001).
Semba et al. 1994b	Randomized, double-blind clinical trial in Indonesia; vit A suppl 2 wk before and 3 wk after TT	n = 139; 3 to 6 y old	<ul style="list-style-type: none"> ■ Children given vit A before TT immunization had significant increases in IgG1 levels, irrespective of whether the response was primary or memory. ■ In children w/ secondary response to TT, vit A caused a modest, but significant change in anti-TT IgG3.
Rosales and Kjolhede 1994	Randomized, double-blind clinical trial; 210-µmol oral dose of retinol or placebo	n = 90 exp; n = 110 cont; 5- mo to 17-y-olds w/ acute measles	<ul style="list-style-type: none"> ■ Children in both groups showed a significant increase in measles antibody titer from baseline to 2 wk after suppl, but the increase was not significantly different between groups (p = 0.25). ■ Vit A did not enhance the immune system in measles.
Semba et al. 1993b	Randomized, double-blind clinical trial in Indonesia; 200,000 IU of vit A	n = 26 exp; n = 29 cont; 3 to 6 y old; 30 w/ and 25 w/o xerophthalmia	<ul style="list-style-type: none"> ■ Children w/ clinical and subclinical VAD receiving suppl had increased numbers of circulating CD4 T cells (p < 0.01) and a higher CD4/CD8 ratio (p < 0.001) 5 wk after suppl. ■ Children w/ xerophthalmia had lower CD4/CD8 ratios (p < 0.08), lower CD4 T cells (p < 0.03), and higher CD8 T cells (p < 0.04) than those w/o xerophthalmia.
Saxon et al. 1993	64-wk open trial of oral 13-cis retinoic acid (RA) for 32 wk	n = 5 patients w/ common variable immunodeficiency (CVI)	<ul style="list-style-type: none"> ■ During the treatment period, circulating IL-6 fell, B-cell size decreased, and B-cell function improved, indicating normalization of humoral immune systems. ■ RA promoted maturation of B cells in patients w/ CVI.

Table 2. Effect of Vitamin A on Immunity (cont.)

Study	Intervention	Sample	Key findings on effect on immunity
Controlled intervention studies			
Lie et al. 1993	1 y randomized, double-blind trial in China; 200,000 IU of vit A + 40 IU of vit E at 3 and 9 mo after baseline	n = 98 exp, n = 74 cont; 6 to 36 mo old	<ul style="list-style-type: none"> ■ Serum retinol and IgA levels were significantly higher in the treatment than in the cont group ($p < 0.01$) 7 wk after first suppl. ■ There was no significant difference in salivary IgA level between the two groups.
Coutsoudis et al. 1992	Randomized, double-blind trial of children w/ measles; 3 doses of up to 200,000 IU	n = 29 exp; n = 31 cont; 4 to 24 mo old	<ul style="list-style-type: none"> ■ The supplemented group showed an increase in total number of lymphocytes (day 42, $p = 0.05$) and measles IgG concentrations (day 8, $p = 0.02$). ■ Vit A did not influence IL-2 or plasma complement levels.
Semba et al. 1992a	Randomized, double-blind clinical trial in Indonesia; oral 200,000 IU of vit A followed 2 wk later by DPT vaccine	n = 118 w/ mild xerophthalmia; n = 118 clinically normal; 3 to 6 y old	<ul style="list-style-type: none"> ■ Clinically normal and xerophthalmic children receiving vit A had greater (>2-fold) IgG responses, both primary and secondary, to tetanus than those who received a placebo ($p < 0.05$). ■ Mild vit A deficient children had a relatively depressed immune response compared w/ supplemented children.
Sidell et al. 1990	1 $\mu\text{g}/\text{kg}/\text{day}$ of 13-cis-RA for 4 mo; TT and KLH immunization	Subjects w/ severe cystic acne; n = 26	<ul style="list-style-type: none"> ■ RA had no effect on immune responses to TT; however, anti-KLH antibody was detected in only 4 of 13 cont compared w/ 10 of 13 RA supplemented subjects ($p < 0.05$) —i.e., anti-KLH response was enhanced in the RA group. ■ In vivo administration of RA can modulate antigen-specific immune responses.
Brown et al. 1980	Field study in rural Bangladesh; high-dose vit A	Children	<ul style="list-style-type: none"> ■ There was no difference in responses to TT or in skin test reactivity to common antigens between vit A treated and cont children.
Animal experiments			
Gangopadhyay et al. 1996	Mice w/ upper respiratory tract infection (influenza A virus)	Vit A deficient ($< 0.35 \mu\text{mol}/\text{L}$) BALB/c mice	<ul style="list-style-type: none"> ■ The influenza-specific salivary IgA response was lower in vit A deficient mice than in ad lib fed cont (0.11% vs. 2.73%, $p < 0.0001$) and, in a separate experiment, in pair-fed cont (0.42% vs. 3.43%, $p < 0.0001$). ■ Influenza-specific salivary IgA secreting plasma cells were fewer in deficient mice than in ad lib or pair-fed cont (3.0% vs. 8.7%, $p < 0.0001$).
Stephensen et al. 1996	Mice fed vit A deficient or cont diet, inoculated w/ influenza virus at 7 or 9 wk of age	Vit A deficient ($\leq 0.35 \mu\text{mol}/\text{L}$) BALB/c mice	<ul style="list-style-type: none"> ■ Influenza-specific salivary IgA response to a mild infection was similar in the deficient (5.3%) and cont (10%) groups ($p > 0.05$); after severe infection, IgA response was lower in deficient mice (0.3%) than in the cont group (4.2%, $p < 0.0001$). ■ IgG response was greater in deficient mice than in cont after both mild and severe infection ($p = 0.0002$).
Molrine et al. 1995	Vit A deficient mice reconstituted w/ human peripheral blood lymphocytes and immunized w/ TT	Severe combined immunodeficient mouse model; 6 to 8 wk old	<ul style="list-style-type: none"> ■ Anti-TT IgG levels were 3.75 $\mu\text{g}/\text{mL}$ in deficient mice compared w/ 148 $\mu\text{g}/\text{mL}$ in cont ($p = 0.0005$). ■ Vit A deficient mice had only a 2.9-fold increase in anti-TT antibody vs. a 74-fold increase in cont ($p < 0.01$). ■ Suppl w/ vit A restored immune responses to normal.

Table 2. Effect of Vitamin A on Immunity (cont.)

Study	Intervention	Sample	Key findings on effect on immunity
Animal experiments			
Chun et al. 1992	Retinol repletion studies in vit A deficient mice; antigen given 24 h postrepletion	Vit A deficient mice	<ul style="list-style-type: none"> ■ Vit A deficient mice fed 4 µg of vit A/g of diet gave an IgG1 response equal to that of vit A sufficient mice. ■ RA was about 10-fold more active than retinyl acetate or retinaldehyde and 100-fold more active than retinol in producing IgG1 response.
Pasatiempo et al. 1992	Vit A depleted rats given 0.1 µg or 1.5 µg of retinol along w/ SSS-III immunization	Vit A depleted Lewis rats	<ul style="list-style-type: none"> ■ Antibody production to pneumococcal polysaccharide (SSS-III) was minimal in depleted rats. ■ 1.5 µg of retinol given as a divided dose (half given 4 days before and half given along w/ immunization) restored antibody production, whereas given as a single dose (along w/ immunization) it was less effective.
Kinoshita et al. 1991	Retinol repletion studies in rats immunized w/TT	Vit A deficient and sufficient rats	<ul style="list-style-type: none"> ■ Rats repleted w/ retinol 1 day after immunization had both primary and secondary IgM and IgG responses similar to vit A sufficient cont. ■ Rats repleted w/ retinol 2 days before the booster immunization had only secondary IgM and IgG responses similar to those of vit A sufficient cont.
Pasatiempo et al. 1991	Retinol repletion studies in rats w/ SSS-III immunization	Vit A depleted and pair-fed cont rats	<ul style="list-style-type: none"> ■ At age 30, 35, and 45 days, serum retinol in vit A depleted rats was 46%, 35%, and 9%, respectively, that of pair-fed cont. ■ Antibody response of vit A depleted rats 35 days old was 22%, and at 45 days old, 8% that of cont ($p \leq 0.001$). ■ The numbers of IgM- or IgD-positive cells or total T cells or helper and suppressor T cell subsets were not affected by vit A status.
Bowman et al. 1990	Rats fed 0 or 4 µg of retinol/g of diet	Vit A depleted and pair-fed cont rats	<ul style="list-style-type: none"> ■ Splenic natural killer (NK) cell activity was 22% to 80% that of cont rats, depending on degree of deficiency. ■ Vit A depleted rats that were repleted w/ oral retinol had consistently normalized NK cell activity. ■ Interferon activity increased from 22% to 33% of cont in deficient rats to 80% to 130% of cont after repletion.
Pasatiempo et al. 1990	Rats fed vit A deficient or adequate diets and immunized w/ bacterial polysaccharide or protein antigens	Male Lewis rats	<ul style="list-style-type: none"> ■ Vit A depletion severely compromised the response to two T-cell-dependent antigens, TT, and sheep RBCs. However, vit A depleted rats immunized w/ polysaccharides had antibody responses similar to vit A sufficient rats.
Pasatiempo et al. 1989	Rats fed 0 or 4 µg of retinol/g of diet, immunized w/ pneumococcal polysaccharide (SSS-III)	Sprague–Dawley and Lewis strains of rats	<ul style="list-style-type: none"> ■ Splenic response to (SSS-III) was 17% of cont ($p = 0.05$) in Sprague–Dawley, and 22% of cont ($p = 0.05$) in Lewis vit A depleted rats. ■ Retinol depletion reduced antibody response to a greater extent in male than in female rats. ■ In both strains of rats, retinol repletion at the time of immunization normalized antibody response.

Table 2. Effect of Vitamin A on Immunity (cont.)

Study	Intervention	Sample	Key findings on effect on immunity
Animal experiments			
Sklan et al. 1989	Chicks fed 0.85 or 350 µg of vit A/kg of diet, plus 1 g/kg of β-carotene and canthaxanthin	Chick model	<ul style="list-style-type: none"> ■ T-lymphocyte proliferative responses were decreased at low vit A intake and enhanced at high vit A intake. ■ Chicks fed β-carotene and canthaxanthin along w/ low vit A diet showed no difference in immune response compared w/ cont, but the proliferative response was enhanced w/ a high vit A diet.
Friedman and Sklan 1989a	Vit A depleted animals fed retinyl acetate boluses	Vit A depleted rats and chicks	<ul style="list-style-type: none"> ■ Vit A depletion led to severe impairment of T-lymphocyte activity in both animal models; this was directly related to vit A status in both animals. ■ Immune response impairment occurred before any other signs of VAD appeared and was rapidly corrected by retinol repletion.
Friedman and Sklan 1989b	Vit A depleted chicks given large bolus of vit A vs. long-term excess of vit A	Vit A depleted chicks	<ul style="list-style-type: none"> ■ Deficiency as well as long-term excess of vit A caused impaired antigen-specific immune response. ■ Immune responsiveness occurred before other signs of hypo- or hypervitaminosis and correlated w/ both hepatic and blood vit A levels. ■ In contrast, vit A suppl of vit A deficient chicks restored normal immune functions.
Hatchigian et al. 1989	6000 IU of vit A palmitate or cont given weekly for 5 wk; infected w/ Salmonella typhimurium	Male Lewis rats; n = 48	<ul style="list-style-type: none"> ■ Cultures of liver and splenic homogenates showed bacteremia in 89% and 100% of infected cont animals vs. 0% and 44% of suppl animals during 1st wk of infection. ■ Kupffer cell, peritoneal, and splenic macrophages of suppl rats had greater phagocytic activity than cont.
Smith et al. 1987	Mice fed vit A deficient diets	Vit A deficient mice	<ul style="list-style-type: none"> ■ Cellular immunity decreased in early deficiency and declined further as deficiency progressed; humoral immunity also declined. ■ Surface expression of membrane glycoproteins and lymphocyte numbers or distribution were unaffected.
Smith and Hayes 1987	Mice fed vit A deficient or suppl diets	Mouse model	<ul style="list-style-type: none"> ■ At age 6 wk, deficient mice immunized w/ a single protein antigen dose produced IgM response similar to suppl mice, but their IgG1 and IgG3 responses were 30% less than the suppl group. ■ At age 8 wk, deficient mice produced 70% as much IgM as the supplemented group, but their IgG1 response was 30% less and IgG3 response was 3% less than supplemented mice; the response kinetics, however, were similar.
Butera et al. 1986	Rats fed vit A deficient and sufficient (pair-fed) diets	Vit A deficient rats, vit A sufficient rats, healthy cont	<ul style="list-style-type: none"> ■ Splenocytes derived from deficient rats had significantly depressed blastogenic response to all mitogens tested; however, thymic lymphocyte blastogenic transformation response was similar in all groups. ■ Mitogen binding to viable cells (splenocytes and thymocytes) was adequate in all groups.

Table 2. Effect of Vitamin A on Immunity (cont.)

Study	Intervention	Sample	Key findings on effect on immunity
Animal experiments			
Nauss et al. 1985	Retinol repletion of vit A deficient rats	Vit A deficient rats	<ul style="list-style-type: none"> ■ Total yield of splenocytes was lower, weights of cervical and mesenteric lymph nodes higher, and splenic pokeweed mitogen responses lower in deficient rats than in supplemented rats.
Ongsakul et al. 1985	Vit A deficient rats injected w/ <i>Escherichia coli</i>	Retinoate-cycled vit A deficient rats	<ul style="list-style-type: none"> ■ Kinetics of blood clearance of <i>E. coli</i> was depressed within 8 days and significantly reduced within 12 days of retinol deficiency. ■ The phagocytic capacity of all deficient animals was less than 40% of cont ($p < 0.01$); deficient animals were more susceptible to endogenous bacterial infection.
Barnett 1983	Mice fed 13-cis-RA in 1 to 4 doses before or after immunization w/ 1 μ g of ovalubumin	BALB/c mouse model	<ul style="list-style-type: none"> ■ An absence of primary antibody response and excellent secondary antibody response were observed in all RA supplemented rats compared w/ cont.
Barnett 1982	Pretreatment of mice w/ 13-cis-RA; immune response to ovalubumin	BALB/c mouse model	<ul style="list-style-type: none"> ■ A single feeding of lower doses (0.3 and 1.5 μg/dose) of RA produced a low IgE response; in contrast, higher doses (3.0 and 6.0 μg/dose) caused a higher, sustained response. ■ Pretreatment w/ RA before immunization produced high sustained secondary titers (titer 360 to 480).
Sirisinha et al. 1980	Rats fed vit A deficient diet	Vit A deficient rats	<ul style="list-style-type: none"> ■ Secretory IgA levels in the intestinal fluid of deficient rats were significantly lower than in cont and were related to duration of VAD. ■ However, there was no difference in the serum antibody response to deoxyribonucleoprotein antigen between the two groups.
Nauss et al. 1979	Rats fed vit A free or suppl diets; ad lib and pair-fed groups	Male Lewis rats	<ul style="list-style-type: none"> ■ Lymphocytes from deficient rats had one-third the transformation response to mitogens, concanavalin A, phytohemagglutinin, and <i>E. coli</i> lipopolysaccharide S; response returned to normal after suppl. ■ Marked leukopenia, decrease in number of lymphocytes, and increase in neutrophils were seen in deficient rats.
In vitro experiments			
Wang et al. 1993	Retinol; Ig synthesis induced by <i>Staphylococcus aureus</i> Cowan I (SAC)	Adult peripheral blood mononuclear cells (PBMC); cord blood mononuclear cells (CBMC)	<ul style="list-style-type: none"> ■ Retinol increased SAC-induced IgM synthesis by CBMC by 5.9-fold and IgG synthesis by adult PBMC by 16.3-fold at retinol concentrations of 1 mM and 10 pM, respectively. ■ Retinol increases Ig synthesis by acting on B cells, whereas effect of RA is mediated by T cells or T-cell products.
Wang and Ballow 1993	RA at 0.1 to 10 pM	Adult PBMC; CBMC	<ul style="list-style-type: none"> ■ RA increased SAC-induced IgG synthesis of adult PBMC even at low concentrations; adult PBMC is 10^4 to 10^6 times more responsive to RA than CBMC. ■ Results suggest that RA increases Ig synthesis of SAC stimulated cultures via its action on T cells, or T-cell products—e.g., cytokines.

Table 2. Effect of Vitamin A on Immunity (cont.)

Study	Intervention	Sample	Key findings on effect on immunity
<i>In vitro</i> experiments			
Blomhoff et al. 1992	RA at 3 mM and 30 nM	Human B lymphocytes	<ul style="list-style-type: none"> ■ RA at 30 nM was less active than at 3 mM in inhibiting growth of normal human B lymphocytes. ■ Retinol at 3 mM inhibited anti-IgM-mediated DNA synthesis by 78%. ■ IL-6 production induced by anti-IgM and IL-4 was markedly reduced by retinol, but induction of IL-6 and tumor necrosis factor was less affected.
Sidell et al. 1991	RA conc. of 10 pM to 10 mM	Myeloma cell line AF10	<ul style="list-style-type: none"> ■ RA reduction of IL-6 receptor was concentration dependent over the range tested and corresponded to the ability of RA to inhibit cell proliferation. ■ The down-regulation of IL-6R by RA was accompanied by reduced IL-6R mRNA expression. ■ Exogenous recombinant IL-6 could overcome RA-induced growth inhibition of AF10 cells.
Israel et al. 1991	RA; stimulation by SAC	Human CBMC; PBMC	<ul style="list-style-type: none"> ■ RA at 0.1 to 10 mM increased IgM synthesis of CBMC in response to SAC by up to 45.6-fold. ■ There were no changes in IgA or IgG synthesis, and the effect on SAC-induced proliferative response was minimal. ■ Similar effects of RA on IgM synthesis were not seen in SAC-stimulated adult PBMC.
Sidell and Ramsdell 1988	RA	Human thymocyte cultures	<ul style="list-style-type: none"> ■ Blastogenesis increased 2- to 4-fold when RA was added to resting thymocytes in the presence of recombinant IL-2 (rIL-2). ■ RA significantly increased the growth rate of long-term rIL-2-dependent thymocyte blasts. ■ RA did not affect peripheral blood lymphocyte response.
Sidell et al. 1984	RA	Human thymocyte cultures	<ul style="list-style-type: none"> ■ RA is required early in the thymocyte activation to phytohemagglutinin. ■ RA induced enhancement of thymocyte proliferation. ■ However, RA did not affect IL-2 production or IL-2-dependent proliferation of T cells.
Sidell et al. 1981	All-trans-RA at 0.1 to 10 mM	Human thymocyte, tonsil lymphocyte cultures	<ul style="list-style-type: none"> ■ Blastogenesis increased up to 2.5-fold when RA was added to human thymocyte or tonsil lymphocyte cultures in the presence of mitogens. ■ No augmentation in proliferative responses of peripheral blood or spleen lymphocytes was observed.
Cohen et al. 1979	In vitro experiments on immune responsiveness after extensive surgical treatment	Lymphocytes from cont vs. vit A treated patients	<ul style="list-style-type: none"> ■ Total lymphocyte count and response in mixed lymphocyte reaction to a pool of stimulating cells were depressed, postoperatively, in cont patients; treatment w/ pharmacologic doses of vit A prevented this depression. ■ Mitogenic activity tended to be higher in patients treated w/ vit A; vit A may be an immunostimulant in humans.

Table 3. Role of Vitamin A in HIV/AIDS Disease

Study	Intervention	Sample	Key findings on role in HIV/AIDS
Case-control studies			
Jolly et al. 1997	Case-control study	n = 26 AIDS hospital vs. clinic patients	<ul style="list-style-type: none"> ■ Mean serum retinol was slightly lower in hospital patients than in clinic attenders. ■ Urinary retinol loss was significantly higher in hospital patients than in clinic attenders (0.09 vs. 0.04, $p = 0.0193$). This loss was significantly predicted by decreased CD4 count ($p = 0.0454$) in clinic patients. ■ Significantly more of those who lost weight died than survived ($p = 0.015$).
Greenberg et al. 1997	Cross-sectional survey in two US cities	n = 133 HIV-infected women w/ infants of known HIV infection status	<ul style="list-style-type: none"> ■ Serum vit A levels measured in the third trimester showed that 16% of transmitting mothers and 6% of nontransmitting mothers had severe VAD ($<0.7 \mu\text{mol/L}$). ■ Severe VAD was associated w/ maternal-infant HIV transmission even after adjusting for CD4⁺ percent and duration of membrane rupture (adjusted OR = 5.05).
Mostad et al. 1997	17-mo cross-sectional study in Kenya	n = 318 HIV-1-infected women	<ul style="list-style-type: none"> ■ VAD was highly predictive of vaginal HIV-1 DNA shedding; after adjusting for CD4 count, severe VAD, moderate VAD, and low normal vit A status were associated w/ 12.9-, 8.0-, and 4.9-fold increased odds of vaginal shedding, respectively. ■ Vit A status may be an important factor in sexual or vertical transmission of HIV-1.
Semba et al. 1997c	Longitudinal cohort study in Malawi	n = 467 HIV-infected women and their children	<ul style="list-style-type: none"> ■ Maternal VAD was independently related to linear ponderal growth (measured until 24 mo old) in children after adjustment for BMI, gender, and HIV status. ■ At 12 mo of age, infants of mothers w/ VAD during pregnancy weighed about 8% less ($p < 0.001$) and were about 2% shorter ($p < 0.001$) than infants of mothers w/o VAD.
Semba et al. 1997b	Prospective, cross-sectional study	n = 284 HIV-infected adult IDUs	<ul style="list-style-type: none"> ■ 28.9% of subjects (38.0% of women and 25.3% of men) were vit A deficient ($p < 0.04$). ■ Plasma vit A level was not significantly correlated w/ infectious viral load in these subjects.
Tang et al. 1997	Nonconcurrent prospective study w/ 9 y of follow-up	n = 311 HIV-seroprevalent men	<ul style="list-style-type: none"> ■ Serum vit A levels were in the normal to high range (median = $2.44 \mu\text{mol/L}$), but there was no consistent association between vit A levels and risk of progression to AIDS. ■ Serum vit A was not associated w/ CD4⁺ cell decline to $<200 \times 10^6$ cells/L or w/ reported intake of multivitamin or single vit A suppl.
John et al. 1997	Cross-sectional survey	212 cervical and 215 vaginal specimens from HIV-seropositive women	<ul style="list-style-type: none"> ■ Detection of vaginal HIV-1 DNA was associated w/ lower CD4 cell count and severe VAD.

Table 3. Role of Vitamin A in HIV/AIDS Disease (cont.)

Study	Intervention	Sample	Key findings on role in HIV/AIDS
Case-control studies			
Semba et al. 1995b	Prospective, cross-sectional study in Malawi	n = 474 HIV-infected mothers and their infants	<ul style="list-style-type: none"> ■ 300 (63.3%) were vit A deficient (<1.05 $\mu\text{mol/L}$). ■ Mean serum vit A in mothers whose infants died were lower than in mothers whose infants survived the first 12 mo of life (0.78 vs. 1.02 $\mu\text{mol/L}$, $p < 0.0001$). ■ Infant mortality rates were 93.3%, 41.6%, 23.4%, 18.5%, 17.7%, and 14.2% among mothers w/ serum vit A levels of <0.35, 0.35 to 0.70, 0.70 to 1.05, 1.05 to 1.40, 1.40 to 1.75, and >1.75 $\mu\text{mol/L}$, respectively ($p < 0.0001$).
Nduati et al. 1995	Cross-sectional study in Kenya	n=107 HIV-1-infected women	<ul style="list-style-type: none"> ■ 58% of the 212 breast milk samples collected had detectable HIV-1 DNA; these samples were more likely to be from women w/ CD4 < 400 (OR = 3.1). ■ Severe VAD (<20 $\mu\text{g/dL}$) was associated w/ a 20-fold increased risk of HIV-1 DNA in breast milk among women w/ low CD4 cell counts (<400/mm^3).
Semba et al. 1995a	4-y case-control, prospective study; mean follow-up period 2.4 y	HIV-infected IDUs; n = 50 dead, n = 235 survivors	<ul style="list-style-type: none"> ■ Among patients who died, 50% had VAD and 38% had wasting in the last visit before death. ■ CD4 cell count < 200/mL, wasting, and VAD were all associated w/ mortality; VAD subjects had higher risk of death (OR = 4.6).
Semba et al. 1994a	Prospective study in Malawi	n = 338 HIV-positive mothers w/infants w/ known HIV status	<ul style="list-style-type: none"> ■ Mother-to-child transmission of HIV was 21.9% in mothers whose infants survived to 12 mo of age. ■ Mothers who transmitted HIV to infants (n =74) had lower serum vit A than those who did not transmit HIV to their infants (0.86 vs. 1.07, $p < 0.0001$). ■ Maternal transmission rates were 32.4%, 26.2%, 16.0%, and 7.2% in mothers w/ serum vit A levels of <0.70, 0.70 to 1.05, 1.05 to 1.40, and >1.40 $\mu\text{mol/L}$, respectively ($p < 0.0001$). ■ Maternal CD4 percent and CD4/CD8 ratio were also associated w/ increased mother-to-child HIV transmission.
Semba et al. 1993a	Longitudinal study; mean follow-up of 22.8 mo	n = 179 subsample of >2000 IDUs	<ul style="list-style-type: none"> ■ More than 15% of the HIV-1-seropositive subjects were vit A deficient (plasma vit A < 1.05 $\mu\text{mol/L}$); HIV-1-seropositive subjects had lower mean plasma vit A than seronegative subjects ($p < 0.001$). ■ VAD was associated w/ lower CD4 counts in both seropositive and seronegative subjects ($p < 0.05$) and increased mortality (RR = 6.3) in seropositive subjects. ■ VAD may be an important risk factor in HIV progression.
Coodley et al. 1993a	Observational study	n = 47 HIV-positive patients	<ul style="list-style-type: none"> ■ Mean serum levels of vit A ($p = 0.04$) and β-carotene ($p = 0.06$) were lower in patients w/ HIV wasting syndrome than in nonwasting patients w/ comparable CD4 cell counts. ■ >10% of HIV-seropositive patients had low serum vit A.
Tang et al. 1993	Cross-sectional survey; mean follow-up of 6.8 y	n = 281 HIV-1-seropositive homosexual men	<ul style="list-style-type: none"> ■ A moderately high dietary intake of vit A (9000 to 20,000 IU/day) was associated w/ reduced progression to AIDS (relative hazard = 0.55).

Table 3. Role of Vitamin A in HIV/AIDS Disease (cont.)

Study	Intervention	Sample	Key findings on role in HIV/AIDS
Case-control studies			
Beach et al. 1992	Longitudinal study	n = 100 HIV-1-infected men; N = 42 men free of HIV; 20 to 55 y old	<ul style="list-style-type: none"> ■ Prevalence of specific nutrient abnormalities was widespread among HIV-1-infected patients. ■ 18% of HIV-1-infected patients had low serum vit A. ■ Similar prevalence of nutrient abnormalities was not seen in HIV-1-seronegative cont.
Controlled intervention studies			
Fawzi et al. 1998b	Vit A (5000 IU + 30 µg of β-carotene/day) or multivitamins w/ or w/o vit A or placebo; randomized, double-blind trial in Tanzania	n = 1075 HIV-1-infected pregnant women (12 to 27 wk gestation)	<ul style="list-style-type: none"> ■ Fetal deaths were higher in women who did not receive multivitamins than in those assigned multivitamins (49 vs. 30, RR 0.61, p = 0.02). ■ Multivitamin suppl decreased risk of low birth weight by 44% (RR 0.56, p = 0.003), severe preterm birth by 39% (RR 0.61, p = 0.03), and small size for gestation age at birth by 43% (RR 0.57, p = 0.002). ■ Vit A alone did not affect any of these variables.
Semba et al. 1998	Randomized, double-blind clinical trial; single dose of 200,000 IU of vit A	n = 120 HIV-infected IDUs	<ul style="list-style-type: none"> ■ Vit A suppl did not have a significant effect on HIV load or CD4 cell count at 2 or 4 wk after suppl.
Coutsoudis et al. 1997	Randomized, double-blind trial in S Africa; 5000 IU of vit A + 30 µg of β-carotene daily until delivery	n = 24 pregnant (28 to 32 wk gestation) HIV-1-infected women	<ul style="list-style-type: none"> ■ Viral load measured at baseline and 1 wk after delivery showed no increase in women receiving vit A, but a significant increase was seen in cont (p = 0.02). ■ Mean change in viral load in the groups was not significantly different (p = 0.31).
Coodley et al. 1996	Prospective, double-blind study; 60 µg of β-carotene 3 times/day; all patients received a multivitamin	n = 72 HIV-positive patients	<ul style="list-style-type: none"> ■ There were no significant differences (p < 0.05) between β-carotene supplemented and cont groups in T-cell subsets, NK cells, or HIV p24 antigen at baseline or after 1 or 3 mo. ■ β-Carotene suppl did not have an effect on immune cells in HIV-infected patients.
Coutsoudis et al. 1995b	Randomized, placebo-controlled trial in S Africa; up to 200,000 IU of vit A	n = 118 children (1 to 15 mo old) of HIV-infected women	<ul style="list-style-type: none"> ■ Among all children, overall morbidity was lower in the vit A supplemented group than in cont (OR = 0.69). ■ Among children w/ known HIV status (28 infected, 57 uninfected), diarrheal morbidity was significantly reduced in vit A supplemented children (OR = 0.51). ■ Diarrheal morbidity was unaffected by vit A in uninfected children.
Saxon et al. 1993	64-wk open trial of oral 13-cis-RA for 32 wk	n = 5 patients w/ common variable immunodeficiency (CVI)	<ul style="list-style-type: none"> ■ During treatment period, circulating IL-6 fell, B-cell size decreased, and B-cell function improved, indicating normalization of humoral immune systems. ■ RA promoted maturation of B cells in patients w/ CVI.
Coodley et al. 1993b	Double-blind clinical trial; 180 µg/day of b-carotene or placebo for 4 wk plus 4-wk crossover	n = 21 HIV-positive patients	<ul style="list-style-type: none"> ■ Total leukocyte count (p = 0.01), percent change in CD4 count (p = 0.02), and percent change in CD4/CD8 ratio (p = 0.02) were higher w/ b-carotene suppl than w/placebo. ■ Absolute CD4 count, absolute CD4/CD8 ratio, and total B lymphocytes increased w/ b-carotene suppl and decreased w/ placebo but were not significantly different.

Table 4. Effect of Vitamin A on Efficacy of Vaccines

Study	Intervention	Sample	Key findings on effect on vaccines
Controlled intervention studies			
WHO/CHD Immunisation-Linked Vitamin A Suppl Study Group 1998	Randomized, double-blind, placebo-controlled trial in Ghana, India, and Peru; 200,000 postpartum to mothers followed by 3 doses of 25,000 IU of vit A w/ DPT/poliomyelitis at 6, 10, and 14 wk	n = 4227 cont; n = 4212 exp	<ul style="list-style-type: none"> ■ 29.1% of infants in the vit A group and 37.1% of cont had serum retinol < 0.7 $\mu\text{mol/L}$ at 6-mo follow-up. ■ This effect was no longer apparent at 9 and 12 mo. ■ A larger proportion of infants in the vit A group than cont had bulging fontanelle, although fewer than 1% of infants in either group were affected. ■ Vit A had no effect on overall or severe morbidity.
Semba et al. 1997a	Randomized, double-blind, clinical trial in Indonesia; 100,000 IU of vit A given at the time of Schwarz measles immunization	n = 394; 9 mo old	<ul style="list-style-type: none"> ■ 37 infants had baseline antibody titers > 1:120, indicating previous natural measles infection; of the remaining infants, 98.8% seroconverted to measles and 99.3% had titers that indicated protection against measles 6 mo postimmunization; seroconversion was similar in both vit A supplemented and cont groups. ■ Vit A can be given at the time of measles immunization in 9-mo-old infants w/o affecting seroconversion.
Stabell-Benn et al. 1997	Randomized, double-blind trial in Guinea-Bissau; 100,000 IU of vit A along w/ measles vaccine given as single dose at 9 mo or two doses at 6 and 9 mo	n = 462 infants followed up to 18 mo of age	<ul style="list-style-type: none"> ■ Simultaneous administration of measles vaccine and vit A did not show any negative effect on measles immunity. ■ Vit A had no significant effect on seroconversion or geometric mean titer (GMT) in children receiving two doses of measles vaccine. ■ In children given one dose of measles vaccine at 9 mo, vit A increased antibody levels (GMT 3704 vs. 2439 mIU, $p < 0.01$), especially in boys.
Stabell-Benn et al. 1995b	Randomized, double-blind, clinical trial in Guinea-Bissau; 100,000 IU of vit A along w/ measles vaccine	n = 78 exp; n = 72 cont; median age 191 days	<ul style="list-style-type: none"> ■ Seroconversion rates did not differ between infants receiving vit A (74%) and placebo (65%, RR adjusted for maternal antibody level was 1.11). ■ In infants who seroconverted, the GMTs were similar in vit A (2896 mIU) and cont groups (2702 mIU); vit A did not have a negative effect on seroconversion to measles vaccine.
Baqi et al. 1995	Randomized, double-blind, trial in Bangladesh; 3 doses of 25,000 IU of vit A at 6.5, 11.8, and 17.0 wk of age	n = 167 infants at DPT/OPV immunization contacts	<ul style="list-style-type: none"> ■ 9 infants (10.5%) from the vit A group and 2 infants (2.5%) from the placebo group had episodes of bulging fontanelle ($p < 0.05$). ■ 12 of the 14 episodes occurred in infants receiving vit A; of these, none occurred w/ the first dose, 3 occurred w/ the second dose, and 9 occurred w/ the third dose. ■ Vit A may have a causal and cumulative effect.
Semba et al. 1995c	Randomized, double-blind, clinical trial in Indonesia; 100,000 IU of vit A given along w/ standard-titer Schwarz measles immunization at 6 mo of age	n = 336; 6 mo old	<ul style="list-style-type: none"> ■ 82% of infants seroconverted to measles. ■ After adjusting for maternal antibody titers, vit A suppl was associated w/ a lower likelihood of seroconversion to measles (OR = 0.40); girls were less likely to seroconvert than boys (OR = 0.34). ■ Concurrent vit A may interfere w/ seroconversion to live measles vaccine in 6-mo-old infants w/ maternal antibody.

Table 4. Effect of Vitamin A on Efficacy of Vaccines (cont.)

Study	Intervention	Sample	Key findings on effect on vaccines
Controlled intervention studies			
Stabell-Benn et al. 1995a	100,000 IU of vit A at 6 mo plus 100,000 IU of vit A at 9 mo, along w/ measles vaccine	6 mo old	<ul style="list-style-type: none"> There was no incidence of bulging fontanelle in infants who received vit A along w/ measles vaccine at 6 and 9 mo of age.
Rahman et al. 1995	Randomized, double-blind, clinical trial in Bangladesh; 3 doses of 25,000 IU of vit A or placebo along w/ DPT/OPV vaccine given monthly	n =101 exp; n =98 cont; 6 to 17 wk old	<ul style="list-style-type: none"> More infants given vit A developed bulging fontanelle; total bulging episodes in the vit A group was 8 compared w/ 1 in the placebo group (RR 7.7, p < 0.04). Fasting retinol level after the third dose was marginally better in the vit A group than in cont (21.9 vs. 19.2, p = 0.05); however, 47% of infants receiving vit A still had low serum vit A (<20 µg/dL).
Agoestina et al. 1994	Placebo-controlled trial in Indonesia; single dose of 50,000 IU of vit A orally	n = 2067 neonates	<ul style="list-style-type: none"> Bulging fontanelle occurred in 2.7% of cont and 4.6% of vit A supplemented infants at 24-h and in 2.4% of cont and 4.5% of the vit A group at 48-h follow-up. None of the infants developed intracranial hemorrhage, and there was no difference between the two groups in resistive index of the anterior cerebral artery, indicating no vit A effect on intracranial pressure.
de Francisco et al. 1993	Randomized, double-blind, trial in Bangladesh; 3 doses of 50,000 IU of vit A at 1.5, 2.5, and 3.5 mo age, along w/ DPT/ poliomyelitis vaccine	n = 191 infants	<ul style="list-style-type: none"> 11 infants (11.5%) in the vit A group and 1 infant (1%) in the placebo group had episodes of bulging fontanelle. 16 of the 17 episodes occurred in infants receiving vit A; a trend toward a cumulative effect of toxicity w/ increasing doses was seen.

Table 5. Effect of Vitamin A During Pregnancy

Study	Study design	Sample	Key findings on effect during pregnancy
Case-control studies			
Mills et al. 1997	Prospective, cross-sectional survey	n = 1508 pregnant women w/ infants w/ or w/o birth defects	<ul style="list-style-type: none"> ■ Women whose pregnancies produced infants w/ NTDs (n = 548) and women w/ infants w/ other major birth defects (n = 387) were not more likely to have consumed 8000 to 10,000 IU vit A/day compared w/ women w/ normal pregnancy outcomes (n = 573). ■ Very few women took large doses (>25,000/day) of vit A. ■ Daily doses of 8000 to 10,000 IU vit A during pregnancy do not appear to cause birth defects.
Yang et al. 1997	Population-based, Atlanta birth defects case-control study	n = 117 infants w/ nonsyndromic limb deficiency; n = 3029 cont	<ul style="list-style-type: none"> ■ Children whose mothers used multivitamins periconceptionally had a lower risk of having a limb deficiency (OR = 0.30, p = 0.05); these multivitamins also contained vit A.
Khoury et al. 1996	Analysis of data from two population-based, case-control studies	n = 47 and 65 NTD cases; n = 3029 and 539 cont	<ul style="list-style-type: none"> ■ A substantial risk reduction was associated w/ periconceptional (-3 to +3 mo) multivitamin (that also contained vit A) use for NTDs (pooled OR = 0.36; p = 0.05).
Botto et al. 1996	Population-based, Atlanta birth defects case-control study	n = 158 infants w/ conotruncal defects; n = 3026 cont	<ul style="list-style-type: none"> ■ Women consuming multivitamin preparations regularly from 3 mo before conception through the 3rd mo of pregnancy had a 43% lower risk of having infants w/ conotruncal heart defects than women who reported no use (OR = 0.57, p = 0.05).
Shaw et al. 1996	Population-based, case-control study of 552,601 deliveries; comparison of women who took vit A w/ those who did not	n > 900 infants w/ malformations	<ul style="list-style-type: none"> ■ For orofacial clefts, no increased risk was associated w/ vit A (10,000 IU/day) supplement use between 1 mo before and 3 mo after conception relative to mothers who used no vit A (OR = 0.55). ■ For conotruncal heart defects, the OR was 0 in mothers who took vit A compared w/ those who did not.
Rothman et al. 1995	Nonrandomized, prospective study; women interviewed for diet and use of vit A supplements during pregnancy	n = 22,748 cohort pregnant women; n = 339 women w/ infants w/ birth defects	<ul style="list-style-type: none"> ■ For vit A from supplements alone, women who took >10,000 IU/day were at increased risk of having infants w/ congenital defects of cranial-neural-crest tissue (RR 4.8; p = 0.05). ■ For vit A from food and supplements, women who took >15,000 IU/day were at increased risk of having infants w/ cranial-neural-crest defects (RR 3.5; p = 0.05). ■ Women consuming high levels of vit A before the 7th wk of gestation appeared to be at particularly high risk. ■ The threshold for supplemental vit A during pregnancy lies near 10,000 IU/day.
Shaw et al. 1995b	Population-based, case-control study of infants w/ conotruncal or limb defects	207 conotruncal cases, 178 limb defect cases, 481 healthy cont	<ul style="list-style-type: none"> ■ Maternal intake of a multivitamin containing folic acid (and vit A along w/ other nutrients) daily during the periconceptional period resulted in a reduced risk for conotruncal (OR = 0.70) and limb (OR = 0.64) defects.
Shaw et al. 1995a	Population-based, case-control study of infants w/ orofacial clefts	731 mothers of infants w/ orofacial clefts, 734 mothers of healthy cont	<ul style="list-style-type: none"> ■ Maternal intake of a multivitamins containing folic acid (and vit A along w/ other nutrients) daily during the periconceptional period resulted in a reduced risk for orofacial clefts (OR = 0.50 to 0.73 depending on cleft phenotype).

Table 5. Effect of Vitamin A During Pregnancy (cont.)

Study	Study design	Sample	Key findings on effect during pregnancy
Case-control studies			
Coutsoudis et al. 1995b	Cross-sectional, prospective study w/ 3 mo follow-up period	54 preterm infants; 24 full-term infants	<ul style="list-style-type: none"> ■ Vit A levels were significantly lower in preterm compared w/ full-term infants (9.81 vs. 15.58 µg/dL, p = 0.0001). ■ Serum retinol and birth weight were positively correlated (r = 0.39; p = 0.0004). ■ Initial vit A levels in preterm infants were not associated w/ respiratory distress syndrome or pneumonia.
Werler and Mitchell 1993	Epidemiological study of women in Boston, Philadelphia, and Toronto	Pregnant women	<ul style="list-style-type: none"> ■ A 60% reduction in risk of NTD birth defects was seen in women taking multivitamin supplements that contained 5000 to 8000 IU of vit A.
Peeples et al. 1991	Cross-sectional survey	n = 67 preterm infants (750 to 1398 g birth weight)	<ul style="list-style-type: none"> ■ At 38 wk postconceptional age (PCA), 48% of infants had plasma retinol levels < 0.35 µmol/L; mean retinol and RBP rose the next 7 mo, but many (44% at 48 wk, 16% at 57 wk) had hyporetinemia (0.35 to 0.67 µmol/L). ■ Plasma RBP plateaued at 57 wk PCA and remained low throughout the first year of life.
Martinez-Frias and Salvador 1990	Hospital-based, case-control study in Spain	Women who were exposed to high doses of vit A during pregnancy	<ul style="list-style-type: none"> ■ Vit A was associated w/ birth defects at levels above 40,000 IU/day (OR = 2.7, p = 0.06); very few women took such high doses of vit A daily in this study population. ■ Vit A does not appear to have adverse effects at levels below 40,000 IU/day (OR = 0.5, p = 0.15). ■ Teratogenic effect of vit A is related to gestation period (OR = 5.4 for 1st and 2nd mo, OR = 1.8 for 3rd mo onward).
Werler et al. 1990	Cross-sectional, case-control study in women from Massachusetts, Pennsylvania, Iowa, and Toronto	n = 5267 pregnant women; n = 2658 infants w/ cranial neural crest defects; n = 2609 cont (infants w/ other defects)	<ul style="list-style-type: none"> ■ In women who consumed multivitamin supplements containing vit A (3333 to 8000 IU), there was no increase in risk of CNS or related birth defects. ■ Women who consumed single vit A supplements plus multivitamins that contained vit A had increased risk of cranial neural crest abnormalities (RR = 2.0). ■ In contrast, women (0.2%) who consumed only vit A supplements were not at a significantly increased risk of birth defects. ■ Congenital malformation was associated w/ vit A suppl (daily use for at least 7 days alone or w/ vit D, or fish oils) during the 1st mo (RR 2.5), 2nd mo (RR 2.3), and 3rd mo (RR 1.6) of pregnancy; relative risk estimates were not significant, and numbers of cases and cont were small.
Mills et al. 1989	Epidemiological study by National Institute of Child Health and Human Development in California and Illinois; women interviewed for use of vit supplements during pregnancy	n = 571 women w/ infants w/ NTD; n = 546 women w/ other birth defect infants; n = 573 women w/ normal infants	<ul style="list-style-type: none"> ■ The rate of periconceptional multivitamin use was similar among the three groups. ■ Periconceptional use of multivitamins did not alter the the risk of having infants w/ NTDs (p > 0.05); the multivitamins contained 5000 to 8000 IU of vit A.

Table 5. Effect of Vitamin A During Pregnancy (cont.)

Study	Study design	Sample	Key findings on effect during pregnancy
Case-control studies			
Milunsky et al. 1989	Epidemiological study in Massachusetts	n = 22,776 pregnant women	<ul style="list-style-type: none"> ■ A 70% reduction in risk of NTD was observed in women consuming multivitamin supplements that contained folic acid and vit A (5000 to 8000 IU). ■ In women who used multivitamins w/o folic acid, the risk of NTD was similar to women who did not use multivitamins during pregnancy.
Mulinare et al. 1988	Epidemiological study by CDC; data from the Atlanta birth defects case-control study	n = 347 infants w/ NTDs; n = 2829 cont	<ul style="list-style-type: none"> ■ Periconceptional multivitamin use among mothers was associated w/ an estimated 60% lower risk of NTD (RR 0.40, p = 0.05); the multivitamins contained 5000 to 8000 IU of vit A.
Hussein et al. 1988	Cross-sectional survey	n = 20 Egyptian pregnant women and neonates	<ul style="list-style-type: none"> ■ Serum vit A in neonates (19.8 µg/dL) was significantly lower than in their mothers (31 µg/dL, p < 0.05); 60% of neonates were vit A deficient (<20 µg/dL). ■ Birth weight of neonates significantly correlated w/ maternal BW (p < 0.001) and cord serum retinol (p < 0.05) but not w/ maternal serum retinol.
Costas et al. 1987	Observational study by NY State Dept. of Health	n = 492 women who delivered infants w/o any birth defects	<ul style="list-style-type: none"> ■ 90.7% of women interviewed reported to have taken some prescription or over-the-counter medication just before and during pregnancy. ■ 81.1% reported taking supplements containing vit A. ■ Only 0.6% reported taking supplements containing >25,000 IU of vit A daily, and 2.6% reported taking supplements containing 15,000 to 24,999 IU of vit A daily.
Zuber et al. 1987	Prospective study	n = 27 pregnant women	<ul style="list-style-type: none"> ■ Mothers who took high doses of vit A (mostly 25,000 IU/day) did not have infants w/ congenital defects.
Rosa et al. 1986	Analysis of several case reports of adverse effects of vit A during pregnancy		<ul style="list-style-type: none"> ■ Maternal use of high-dose vit A supplements (>25,000 IU/day) during pregnancy was associated w/ craniofacial, CNS, cardiac, urinary, and skeletal malformations; long-term megadoses of vit A should be avoided in fertile women.
Lammer et al. 1985	Case-control study	n = 154 pregnant women; subset of n = 36 observed prospectively	<ul style="list-style-type: none"> ■ Exposure to 13-cis-RA was associated w/ a high risk of selected major malformations (RR 25.6); abnormalities of craniofacial, cardiac, thymic, and central nervous systems were observed.
Gebre-Medhin and Vahlquist 1984	Comparison study between Sweden (w/ lowest perinatal mortality rate of 10.6/1000 births) and Ethiopia (66/1000 births)	n = 39 Swedish, n = 49 Ethiopian fetal and newborn postmortems	<ul style="list-style-type: none"> ■ Median liver vit A was higher in Swedish (37.0 µg/g) than in Ethiopian fetuses (9.1 µg/g, p < 0.001). ■ Liver vit A increased exponentially in Swedish fetuses during 2nd and 3rd trimesters of pregnancy; this trend was not seen in Ethiopian fetuses.
Winship et al. 1984	Population-based, case-control study in England	n = 764 mothers w/ infants w/ CNS defects; n = 764 cont	<ul style="list-style-type: none"> ■ Maternal intake of multivitamins containing folic acid was associated w/ a 60% lower risk of CNS defects in the offspring; the multivitamins contained about 3000 to 5000 IU of vit A.

Table 5. Effect of Vitamin A During Pregnancy (cont.)

Study	Study design	Sample	Key findings on effect during pregnancy
Case-control studies			
Wallingford et al. 1983	Cross-sectional survey	Pregnant women, n = 25 w/ normal outcome, n = 14 w/ abnormal outcome	<ul style="list-style-type: none"> ■ Retinol levels in amniotic fluid from 20 wk of gestation onward was significantly greater than at 16 to 18 wk. ■ RBP in amniotic fluid was in excess of, and significantly correlated w/, retinol in amniotic fluid ($p < 0.001$). ■ Retinol in amniotic fluid in pregnancies that ended in birth defects ranged from 2.3 to 18.0 $\mu\text{g}/\text{dL}$ at 16 to 18 wk of gestation; retinol or RBP cannot be used as a marker for prenatal diagnosis of abnormalities.
Lewis et al. 1942	Cross-sectional study on newborn infants fed a vit A free diet	n = 15 newborn infants	<ul style="list-style-type: none"> ■ Blood vit A rose spontaneously in 91% of infants from 24 USP units at 1 to 3 days to 47 United States Pharmacopeia units/100 mL at 6 to 9 days of age, despite consumption of a vit A free diet.
Controlled intervention studies			
Czeizel 1996	Randomized, double-blind, controlled trial in Hungary; multivitamin or trace element suppl daily periconceptionally	n = 2471 multi-vitamin; n = 2391 trace element	<ul style="list-style-type: none"> ■ After excluding infants w/ NTDs, the rate of major congenital abnormalities was significantly higher in the trace element group than the multivitamin group (RR 0.54, $p = 0.0003$); multivitamin suppl decreased the rate of urinary tract and cardiovascular abnormalities.
Agoestina et al. 1994	Placebo-controlled trial in Indonesia; single dose of 50,000 IU of A vit A orally	n = 2067 neonates	<ul style="list-style-type: none"> ■ Bulging fontanelle occurred in 2.7% of cont and 4.6% of vit A supplemented infants at 24-h, and 2.4% of cont and 4.5% of the vit A group at 48-h follow-up. ■ None of the infants developed intracranial hemorrhage, and there was no difference between the two groups in resistive index of the anterior cerebral artery, indicating no vit A effect on intracranial pressure.
Czeizel et al. 1994	Randomized, controlled trial; multivitamin having 0.8 μg of folic acid during periconceptional period	n = 5502 pregnant women	<ul style="list-style-type: none"> ■ Periconceptional multivitamin suppl increased fertility, but had no significant effect on the rate of fetal deaths, birth weight, or preterm birth in singletons. ■ Multivitamin suppl decreased the occurrence and recurrence of NTDs.
Czeizel and Dudas 1994	Randomized, controlled trial; multivitamin or trace element suppl daily periconceptionally	Pregnant women n = 2471 multi-vitamin; n = 2391 trace element	<ul style="list-style-type: none"> ■ Women receiving the multivitamin supplements had no incidence of infants w/ NTDs, whereas the group receiving trace element supplements had 6 offspring w/ NTDs ($p = 0.0014$). ■ Congenital malformations were more prevalent in the trace element group than in the multivitamin group (2.22 vs. 1.25 per 1009; $p = 0.002$).
Czeizel 1993	Randomized, prospective study; periconceptional multivitamin or trace element suppl	n = 4753 pregnant women	<ul style="list-style-type: none"> ■ Periconceptional multivitamin suppl had no beneficial effect on fetal death. ■ In 2104 vit and 2052 trace element informative pregnancies, the rate of congenital abnormalities was greater in the trace element group than in the multivitamin group (22.4 vs. 13.3 per 1000).

Table 5. Effect of Vitamin A During Pregnancy (cont.)

Study	Study design	Sample	Key findings on effect during pregnancy
Controlled intervention studies			
Czeizel and Dudas 1992	Randomized, controlled trial in Hungary; women given multivitamins or trace element supplement during periconceptual period	n = 4753 pregnant women	<ul style="list-style-type: none"> ■ Women consuming multivitamins (containing 4000 to 6000 IU of vit A, 0.8 µg of folic acid, and other nutrients) had a lower incidence of spina bifida, anencephaly, and other birth defects compared w/ the trace element group (22.9 vs. 13.3 per 1000, p = 0.02). ■ 6 cases of NTDs were seen in the trace element group compared w/ none in the multivitamin group (p = 0.029).
Dudas and Czeizel 1992	Randomized, controlled trial in Hungary; women given multivitamins or placebo daily during pregnancy	Pregnant women; n = 1203 exp; n = 1510 cont	<ul style="list-style-type: none"> ■ Women taking multivitamin supplements had no infants w/ NTDs, whereas the placebo group had 6 infants w/ NTDs (p < 0.05); the overall rate of birth defects was also lower in the multivitamin group; the vit A content of the multivitamin was 6000 IU.
Medical Research 1991	Randomized, multi-national, double-blind study among women in England, Israel, Australia, Canada, USSR, Hungary, and France	n = 1817 women at high risk of NTD; suppl w/ folic acid, 7 other vitamins (incl. 4000 IU of vit A), both, or neither	<ul style="list-style-type: none"> ■ Infants of mothers who took folic acid supplements had a 72% lower incidence of NTD (RR 0.28, p = 0.05); a Council similar reduction was also seen in women who took both vitamins plus folic acid. ■ In contrast, in mothers who took vitamins alone, risk of NTDs was similar to placebo group (RR 0.80; p = 0.05).
Schorah and Smithells 1991	Analysis of 6 separate randomized intervention trials in the UK	n = 673 women supplemented w/ and n = 696 women not supplemented w/ multivitamins	<ul style="list-style-type: none"> ■ Women taking multivitamin supplements that contained vit A, among other nutrients, had an 80% reduction in the rate of NTD birth defects
Seller and Nevin 1984	Randomized, controlled trial in SE England and N Ireland	Pregnant women w/ history of NTD supplemented w/ multivitamins periconceptionally	<ul style="list-style-type: none"> ■ Periconceptual vit therapy resulted in about a 2-fold reduction in the recurrence risk of NTD in SE England and about a 3-fold reduction in N Ireland compared w/ unsupplemented women. ■ Benefits of periconceptual vit treatment are more marked in the high NTD prevalence area.
Smithells et al. 1983	Population-based study; mothers w/ a history of NTDs supplemented w/ multivitamins periconceptionally	n = 254 mothers suppl; n = 219 cont	<ul style="list-style-type: none"> ■ Supplemented mothers had fewer recurrences of NTD (0.9%) compared w/ unsupplemented mothers (5.1%); multivitamins contained vit A along w/ other nutrients.
Case reports			
Roche Working Group 1993	Cases reported to Hoffmann-La Roche, Ltd.		<ul style="list-style-type: none"> ■ A fetus w/ spina bifida was reported to be associated w/ an unknown dose and duration of therapy w/ a Roche drug, Supradyn (25,000 IU of vit A and folic acid). ■ Bilateral club feet reported in an infant of mother treated w/ an unknown dose of a Roche drug, Arovit (retinyl palmitate), and fluoride during pregnancy. ■ Stillbirth of an infant to a mother treated w/ Arovit (50,000 IU/day) for acne during the 1st mo of pregnancy. ■ Induced abortion of fetus w/ hydrocephalus in a mother treated w/ Arovit (dose and duration unknown).

Table 5. Effect of Vitamin A During Pregnancy (cont.)

Study	Study design	Sample	Key findings on effect during pregnancy
Case reports			
Lungarotti et al. 1987	Case report		<ul style="list-style-type: none"> ■ Woman supplemented w/ 2000 IU of vit A daily during pregnancy gave birth to an infant w/ multiple malformations; the woman also reported to have consumed orange vegetables and liver during pregnancy.
Von Lennep et al. 1985	Case report		<ul style="list-style-type: none"> ■ Mother consuming 150,000 IU of retinyl esters daily during pregnancy from day 14 to 21 of gestation had a child w/ partial sirenomelia.
Strange et al. 1978	Case report		<ul style="list-style-type: none"> ■ Woman consuming 150,000 IU of retinyl esters daily during pregnancy from day 19 to 40 of gestation had an infant w/ a birth defect (microhydrocephaly).
Mounoud et al. 1975	Case report		<ul style="list-style-type: none"> ■ Case report of a 2½-y-old boy w/ Goldenhar syndrome (congenital malformation) whose mother accidentally consumed 10 mL of an oily solution of vit A (estimated to contain 500,000 IU) in her 2nd mo of pregnancy.
Bernhardt and Dorsey 1974	Case report		<ul style="list-style-type: none"> ■ Mother taking a fish liver oil product daily (reported to contain 25,000 IU of vit A for the first 3 mo of gestation and 50,000 IU for the remainder of gestation) gave birth to a child w/ an aberrant ureter, which was dilated and entered the vagina.
Pilotti and Scorta 1965	Case report		<ul style="list-style-type: none"> ■ Mother consuming 40,000 IU of retinol together w/ 600,000 IU of vit D during the first trimester had an infant w/ malformations of the urinary tract.
Animal experiments			
Biesalski et al. 1996	Rat model: maintenance diet enriched w/ 15.2 × 10 ³ RE/kg at start and increased stepwise to 52.5 × 10 ³ for 8 mo; cont group: 4.5 × 10 ³ RE/kg	n = 20 exp, n = 10 cont than in mothers	<ul style="list-style-type: none"> ■ With high vit A intake, retinol metabolites, 4-oxo- and 5,6-epoxy-RA levels were significantly higher in fetuses (p < 0.001). ■ High intakes of vit A by rat dams resulted in high levels of maternal and fetal plasma vit A and its metabolites; however, no fetal malformations were observed; circulating retinyl esters may not be teratogenic.

Table 5. Effect of Vitamin A During Pregnancy (cont.)

Study	Study design	Sample	Key findings on effect during pregnancy
Animal experiments			
Ritchie et al. 1992	In vitro experiments of vit A metabolites		<ul style="list-style-type: none"> ■ Single exposure to high doses of vit A appeared to present no risk. ■ Exposure to vit A at a level above the threshold for teratogenicity must occur during the entire critical period of development for vit A to induce teratogenicity.
Sharma and Misra 1988, 1987	Rats fed low, medium, and adequate (6, 40, and 100 µg of retinol/day/kg of BW, respectively) vit A	Pregnant rats and their pups	<ul style="list-style-type: none"> ■ Marginal VAD in rat dams was associated w/ severe congenital malformations of the heart and lungs of their offspring.
Vorhees et al. 1978	Sprague–Dawley rats given 80,000 IU of vit A per kg of BW during gestation	Pregnant rats and their pups	<ul style="list-style-type: none"> ■ Significant adverse effects of vit A excess were seen on weight gain, locomotor activity, and maze learning ability of offspring.
Vacca and Hutchings 1977	Pregnant rats given a teratogenic dose of vit A on days 17 and 18 of gestation	Pregnant rats and their pups	<ul style="list-style-type: none"> ■ Vit A excess temporarily interferes w/ early neurogenesis, which resulted in permanent behavioral deficits in adulthood despite cytochemical repair.
Palludan 1976	Pigs fed vit A deficient diet	Pregnant pigs and offspring	<ul style="list-style-type: none"> ■ VAD had adverse effects on fetal development, especially eye organogenesis, in pigs.

Table 6. Effect of Vitamin A During Lactation

Study	Study design	Sample	Key findings on effect during lactation
Cross-sectional survey			
Brown et al. 1986	Cross-sectional survey in Bangladesh	Lactating women	<ul style="list-style-type: none"> ■ Volume of breast milk and composition of breast milk were related to maternal nutritional status; malnourished mothers had reduced output and lower nutritive quality of breast milk.
Gebre-Medhin et al. 1976	Comparison study between Swedish (adequate intake of retinol) and Ethiopian (poor diet) women	Lactating women	<ul style="list-style-type: none"> ■ Breast milk vit A over the same lactation period (0.5 to 6.5 mo postpartum) was higher in the Swedish mothers (467 µg/L) than in the Ethiopian mothers (298 µg/L); comparable differences in plasma RBP were also seen. ■ Breast milk retinol constituted 3.5% of total vit A in milk in Swedish mothers, and 15% to 30% in Ethiopian mothers.
Controlled intervention studies			
Roy et al. 1997	Prospective, randomized controlled study in Bangladesh; 209 µmol of vit A or placebo given 24 h after delivery	n = 50 low-income pregnant women in their last trimester; 16 to 35 y old	<ul style="list-style-type: none"> ■ Mean serum retinol increased in supplemented mothers compared w/ cont (2.77 vs. 1.15 µmol/L, p < 0.05) and remained higher than in cont up to 3 mo after suppl. ■ Breast milk retinol was also greater in the suppl group than in cont for up to 6 mo after suppl (p < 0.02). ■ Infants of supplemented mothers had reduced mean duration of respiratory tract infection (3.1 vs. 3.7 days, p < 0.03) and mean incidence of febrile illness (0.1 vs. 0.3 day, p < 0.002), compared w/ cont.
Stoltzfus et al. 1993	Randomized, double-blind trial in Indonesia; 312 µmol of vit A or placebo 1 to 3 wk postpartum	n = 153 mothers	<ul style="list-style-type: none"> ■ Serum retinol levels were higher in the vit A group than in cont at 3 mo (1.39 vs. 1.24 µmol/L, p = 0.03) and at 6 mo postpartum (1.23 vs. 1.08 µmol/L, p = 0.03). ■ Breast milk retinol was also higher in the vit A group than in the placebo group by 0.48 to 1.18 µmol/L at 1 to 8 mo postpartum (p < 0.05). ■ At 6 mo of age, infants of vit A supplemented mothers had lower prevalence of low serum retinol (<0.52 µmol/L; 15% vs. 36%, p < 0.005) and low vit A stores (10% vs. 23%, p < 0.03) compared w/ infants of cont mothers.
Bates 1983	Intervention trial; 1250 µg/day of preformed vit A as vit-fortified tea drink to all lactating women in Keneba, Gambia	Lactating women	<ul style="list-style-type: none"> ■ Plasma retinol was slightly higher in suppl group (n = 47) than in nonsuppl group (n = 29) during the entire course of lactation. ■ The vit A content of foremilk tended to be higher in supplemented (535 µg/L, n = 27) than in nonsupplemented mothers (525 µg/L, n = 38); difference not significant. ■ Plasma retinol levels in the Gambian mothers were significantly lower when compared w/ a parallel group of Caucasian women in England.
Kon and Mawson 1950	Intervention trial; up to 7200 µg of vit A per day during pregnancy or at parturition	Pregnant women	<ul style="list-style-type: none"> ■ Suppl w/ vit A at 900 to 3600 µg/day for 1 wk to 3 mo during pregnancy did not affect breast milk retinol. ■ Suppl w/ vit A at 7200 µg/day for 9 days immediately after parturition increased vit A in the fat of breast milk by 40% to 70%.

Table 7. Interaction of Vitamin A with Iron and/or Zinc

Study	Study design	Sample	Key findings on vitamin A and iron/zinc interactions
Animal experiments			
Roodenburg et al. 1996	Rats fed iron adequate (35 µg/kg) diets w/ 1, 75, 150, 450, or 1200 RE/kg of feed for 5 wk, followed by vit A and iron repletion w/ impaired vit A status.	Male rats	<ul style="list-style-type: none"> ■ In rats fed diets w/o vit A, vit A suppl raised mean cell volume, plasma iron, and total iron binding capacity; vit A suppl during iron repletion decreased iron in spleen and tibia. ■ Suppl w/ vit A during iron repletion may contribute to optimum erythropoiesis and iron mobilization in rats
Roodenburg et al. 1994	Rats fed either cont diet (35 µg of iron and 1200 RE/kg of feed), vit A free diet, or low-iron diet.	Male rats	<ul style="list-style-type: none"> ■ During 10-wk follow-up, neither iron nor VAD caused any clinical signs; VAD resulted in mild anemia followed by a rise in iron absorption and splenic iron and a decrease in TIBC.
Van Houwelingen et al. 1993	Rat model; 0 or 4000 IU of vit A/kg of diet	Female and male Wistar rats; 21 days old	<ul style="list-style-type: none"> ■ Vit A restriction decreased plasma retinol, blood hemoglobin, and hematocrit. ■ VAD lowered heart zinc levels but only when copper was also restricted in the diet.
Sijtsma et al. 1993	Rats fed diets w/ 0 or 120 (low) or 1200 (high) RE/kg of feed for 28 days	Male rats	<ul style="list-style-type: none"> ■ Plasma retinols were decreased in rats fed low vit A diets, but no changes were seen in BW or feed intake. ■ Marginal VAD slightly lowered blood hemoglobin levels; and increased liver iron concentration. ■ Efficiency of iron absorption was increased; bone marrow iron uptake may be depressed in marginal VAD.
Beynen et al. 1992	Rats fed diets w/ 0 (low) or 4000 (high) IU of vit A/kg of feed for 28 days	Male rats	<ul style="list-style-type: none"> ■ BW and plasma retinol were significantly decreased in rats fed low vit A diets. ■ Marginal VAD significantly lowered hemoglobin levels but did not affect hematocrit values. ■ Liver iron was significantly higher w/ low vit A diets.
Staab et al. 1984	Rats fed various levels of vit A and/or iron for 6 wk	Weanling rats	<ul style="list-style-type: none"> ■ Low dietary iron, but not low vit A, lowered hemoglobin, hematocrit, and RBC counts. ■ High dietary iron was associated w/ lower liver vit A. ■ High vit A diet significantly lowered liver iron even when dietary iron was high; vit A may be important for release of iron from the liver.
Mejia et al. 1979	Rats fed diets sufficient or deficient in vit A	Postweaning rats weighing 150 g	<ul style="list-style-type: none"> ■ Blood hemoglobin and hematocrit values dropped before any signs of severe VAD appeared. ■ Data suggest that anemia may be a component of vit A deficiency, but it may be masked by dehydration that occurs in severe VAD.
Cross-sectional surveys			
Ahmed et al. 1993b	Cross-sectional study in Bangladesh	n = 242; 5 to 12 y old	<ul style="list-style-type: none"> ■ Mean serum zinc levels were lower in children w/ serum retinol concentrations < 0.7 µmol/L than in those w/ concentrations > 0.7 µmol/L.
Wolde-Gebriel et al. 1993	In-depth cross-sectional survey in Shoa Region, Ethiopia	n = 344 school-children chosen from a cohort of 14,740	<ul style="list-style-type: none"> ■ Mean hemoglobin levels were strongly correlated w/ other indices of iron status (MCHC, PCV, RBC count) and serum retinol concentrations; the relationship was at least as strong as the relationship between serum ferritin and blood hemoglobin or TS.

Table 7. Interaction of Vitamin A with Iron and/or Zinc (cont.)

Study	Study design	Sample	Key findings on vitamin A and iron/zinc interactions
Cross-sectional surveys			
Suharno et al. 1992	Cross-sectional study in West Java, Indonesia	n = 318 pregnant women	<ul style="list-style-type: none"> ■ 49% of women were anemic, 43% had iron deficiency anemia, 22% had iron-deficient erythropoiesis, and 6% had iron depletion; 31% of them had marginal vit A status, and 2.5% were vit A deficient. ■ Serum retinol was positively correlated ($p < 0.01$) w/ hemoglobin, hematocrit, and serum iron levels. ■ Suboptimal vit A status was associated w/ nutritional deficiency anemia.
Udomkesmalee et al. 1990	Observational study in NE Thailand schoolchildren	n = 283; 7- to 13-y-old	<ul style="list-style-type: none"> ■ Serum vit A levels of $<0.86 \mu\text{mol/L}$ were seen in more than one-quarter of the children; about 71% of children had low serum zinc levels ($<10.7 \mu\text{mol/L}$), and 23% had both low serum vit A and zinc. ■ Serum zinc was significantly correlated w/ RBP ($p < 0.001$) but not w/ serum retinol.
Bloem et al. 1989	Cross-sectional study and intervention trial in NE Thailand	n = 1060; 1 to 8 y old	<ul style="list-style-type: none"> ■ Retinol was significantly associated w/ hematocrit, ferritin, serum iron, transferrin, and percent TS. ■ Among children w/ hemoglobin $< 7.5 \mu\text{mol/L}$, those receiving vit A capsules (n = 78) for 2 mo showed an increase in retinol, RBP, serum iron, and percent TS, compared w/ those not receiving vit A capsules (n = 88). ■ Periodic large-dose vit A suppl may improve iron status.
Hodges et al. 1978	Study of exp human VAD; vit A depletion period followed by repletion	n = 8 middle-aged male volunteers	<ul style="list-style-type: none"> ■ Vit A depletion diets fed for 400 days caused a rapid decrease in serum carotene and a slower decrease in serum vit A. ■ A daily intake of 18 to 19 μg of iron did not prevent a gradual manifestation of mild anemia during vit A depletion; additional iron therapy did not prevent anemia as long as VAD persisted. ■ Serum retinol was positively correlated w/ blood hemoglobin ($p < 0.01$).
Mejia et al. 1977	Retrospective study of six surveys conducted by INCAP	1 to 12 y old	<ul style="list-style-type: none"> ■ In children 5 to 12 y old, hemoglobin was positively correlated w/ plasma retinol; a positive correlation between serum retinol and iron was seen in all children. ■ Percent TS lower when plasma retinol levels were low. ■ A possible relationship between VAD and anemia exists.
Controlled intervention studies			
Layrisse et al. 1997	Controlled intervention trial; precooked maize flour fortified w/ 9500 IU of vit A and 50 μg of iron/kg	n = 94 adults	<ul style="list-style-type: none"> ■ Nonheme iron absorption from maize bread given along w/ coffee or tea was not significantly different from breakfast w/o coffee or tea, indicating that vit A diminished the inhibitory effects of coffee or tea on iron absorption. ■ In vitro studies indicate that vit A binds iron in the digestive tract and keeps it in a soluble form.

Table 7. Interaction of Vitamin A with Iron and/or Zinc (cont.)

Study	Study design	Sample	Key findings on vitamin A and iron/zinc interactions
Controlled intervention studies			
Angeles-Agdeppa et al. 1997	Intervention trial in Indonesia; weekly or daily micronutrient suppl for 2 or 3 mo	n = 273 adolescents	<ul style="list-style-type: none"> ■ 2 mo after suppl, groups receiving micronutrients weekly and daily showed similar improvements in retinol and hemoglobin levels; suppl for 2 or 3 mo had similar results. ■ Weekly suppl w/ 60 µg of iron and 6000 µg of retinol for 3 mo improved iron status for about 9 mo in adolescents.
Northrop-Clewes et al. 1996	Randomized trial near Peshawar, Pakistan; 15 µg/day of iron or placebo for 3 mo	n = 300 breast-fed infants < 2 y old	<ul style="list-style-type: none"> ■ Infants receiving iron showed increases in hemoglobin, ferritin, and the acute-phase protein ACT. ■ Vit A status improved in both groups. ■ Among infants receiving iron, the increase in serum retinol was associated w/ a decrease in ACT, ferritin, IgA, and IgM, suggesting an anti-infective role for vit A against the potentially toxic effects of iron.
Katelhut et al. 1996	Randomized controlled intervention in Indonesia; 60 µg of iron + 500 µg of folate + 20,000 IU of vit A + 60 µg of vit C or 60 µg of iron + 250 µg of folate weekly for 5 wk	n = 84 adolescents w/ hemoglobin ≤14 g/L	<ul style="list-style-type: none"> ■ Hemoglobin, mean cell volume, and serum ferritin rose significantly in both groups (p < 0.05). ■ Among anemic subjects, the rise in hemoglobin in the multisupplement group was higher than that in the iron and folate group, indicating that vitamins A and C w/ iron provide additional improvement in iron status.
Suharno et al. 1993	Randomized, double-blind trial in West Java, Indonesia; 2.4 µg of retinol, 60 µg of iron or both, or placebo daily for 8 wk	n = 251 pregnant women; 17 to 35 y old; 16 to 24 wk gestation	<ul style="list-style-type: none"> ■ Highest hemoglobin levels (12.78 g/L) were seen in women receiving both vit A and iron, w/ one-third of the response attributable to vit A (3.68 g/L) and of two-thirds attributable to iron (7.71 g/L). ■ After suppl, the proportion of nonanemic women was 35% in the vit A group, 68% in the iron group, 97% in the vit A + iron group, and 16% in the placebo group.
Udomkesmalee et al. 1992	Randomized, double-blind trial in NE Thailand; suppl w/ 25 µg of zinc, or 1500 RE, or zinc + vit A, or placebo daily for 6 mo	n = 133 children 6 to 13 y old w/ marginal plasma retinol (<1.05 µmol/L) and zinc (<12.2 µmol/L)	<ul style="list-style-type: none"> ■ Both vit A and zinc status increased significantly after suppl w/ zinc plus vit A. ■ Zinc suppl improved symptoms related to vision. ■ Combined suppl w/ vit A and zinc normalized conjunctival epithelium as measured by CIC.
Bloem et al. 1990b	Randomized, controlled trial in NE Thailand; single oral dose of 200,000 IU of vit A or placebo	n = 134 school-children; 3 to 9 y old	<ul style="list-style-type: none"> ■ 2 wk after suppl, serum retinol, RBP, hemoglobin, hematocrit, serum iron, and TS rose significantly in the supplemented group compared w/ cont. ■ Serum ferritin levels did not change significantly. ■ A causal association between vit A and iron may exist.
Panth et al. 1990	Intervention trial; 1800 µg of vit A/day for >12 wk	n = 450 pregnant women	<ul style="list-style-type: none"> ■ Vit A suppl prevented the decline in plasma vit A that is normally seen in the last few weeks of pregnancy. ■ Vit A levels in cord blood also increased w/ vit A suppl. ■ Vit A suppl along w/ iron prevented the significant decline in hemoglobin occurring at 26 to 28 wk of gestation.

Table 7. Interaction of Vitamin A with Iron and/or Zinc (cont.)

Study	Study design	Sample	Key findings on vitamin A and iron/zinc interactions
Controlled intervention studies			
Mejia and Chew 1988	Randomized, controlled study; 10,000 IU of vit A, 3 µg of iron/kg of BW/day, or both, or placebo for 2 mo	n = 99 anemic children; 1 to 8 y old	<ul style="list-style-type: none"> ■ Vit A treatment increased retinol, hemoglobin, iron, hematocrit, RBC count, and % TS in serum but did not affect transferrin iron binding capacity or serum ferritin. ■ Combined vit A and iron treatment resulted in a better response of serum iron and percent TS compared w/ vit A or iron treatments alone.
Muhilal et al. 1988a	Controlled trial of monosodium glutamate (MSG) fortification w/ 810 µg of RE/g in Indonesia	5 cont villages; 5 exp villages	<ul style="list-style-type: none"> ■ MSG retained 84% of the vit A potency after 4 mo and 57% after 11 mo in the market. ■ Serum vit A levels significantly increased in exp villages from 0.67 at baseline to 0.92 µmol/L at 11 mo follow-up (p < 0.001). ■ Breast milk vit A rose from 0.60 at baseline to 0.67 µmol/L at 11 mo follow-up (p < 0.05) in exp villages. ■ No changes in serum or breast milk vit A were seen in cont villages.
Muhilal et al. 1988b	Controlled trial of MSG fortification w/ 810 µg of RE/g in 10 villages in Indonesia	Children; 5 exp villages; 5 cont villages	<ul style="list-style-type: none"> ■ Prevalence of Bitot's spots fell from 1.2% at baseline to 0.2% at 11-mo follow-up among children in exp villages. ■ Hemoglobin levels rose by 10 g/L within 5-mo follow-up; linear growth was greater among children in exp villages compared w/ cont villages. ■ Mortality rate was 1.8 times higher in cont villages.
Mejia and Arroyave 1982	Longitudinal study of national fortification of sugar w/ vit A in Guatemala	Preschoolers	<ul style="list-style-type: none"> ■ At 6 mo after fortification, a positive correlation was seen between changes in vit A status and iron status. ■ At 2 y after fortification, serum retinol, RBP, iron, percent TS, and ferritin were significantly increased (p < 0.05).
Arroyave et al. 1981	Longitudinal study of the national sugar/vit A fortification program in Guatemala	Preschoolers	<ul style="list-style-type: none"> ■ After 1 y of fortification, serum retinol significantly rose in 76% of the children; 100% of the children w/ initial values of <20 µg/dL showed an increase from 16.2 to 30.2 µg/dL (p < 0.00001). ■ Similar positive effects on vit A status were seen after 2 y of fortification.
Shingwekar et al. 1979	Intervention trial in India; suppl w/ 40 µg of zinc daily for 5 to 10 days	n = 45 children w/ VAD; n = 20 children w/ PEM; n = 30 cont	<ul style="list-style-type: none"> ■ Plasma vit A, RBP, and zinc were significantly lower in children w/ VAD or PEM, compared w/ cont. ■ Suppl w/ zinc significantly increased plasma vit A and RBP levels in children w/ PEM but not VAD. ■ In children w/ PEM, zinc deficiency may contribute to lowered plasma vit A levels.
Mohanram et al. 1977	Hematological studies; suppl w/ 8 µg of retinol palmitate for 2 to 3 wk	n = 110 children w/ various levels of plasma retinol	<ul style="list-style-type: none"> ■ Hemoglobin and hematocrit were lower in children w/ plasma retinol < 20 µg/dL compared w/ those w/ >20 µg/dL. ■ Suppl w/ vit A increased hemoglobin, hematocrit, and plasma iron. ■ VAD may contribute to anemia in children.

Table 8. β -Carotene As a Source of Vitamin A

Study	Intervention	Sample	Key findings on β -carotene as a source of vitamin A
Intervention studies			
de Pee et al. 1998	Trial in West Java, Indonesia; 3.3 μ g/day of β -carotene as animal foods, 3.0 μ g/day as orange-colored fruit, 4.1 μ g/day as DGLV and carrots, or placebo given 6 days/wk for 9 wk for 1 RE.	n = 238 anemic schoolchildren; 7 to 11 y old	<ul style="list-style-type: none"> ■ Serum retinol increased significantly in all 3 treatment groups; compared w/ cont, the difference was greater in retinol-rich animal food and fruit groups ($p < 0.001$) than in the vegetable group ($p < 0.01$). ■ Results indicate that 1 RE is equivalent to 12 μg of β-carotene for fruit and 26 μg for DGLV and carrots rather than the conventional conversion factor of 6 μg of β-carotene
Jalal et al. 1998	Trial in Indonesia; 5.1 μ g/day of β -carotene as red sweet potato or GLV w/ or w/o deworming versus placebo	n = 242; 2 to 7 y old	<ul style="list-style-type: none"> ■ Serum retinol increased after consumption of β-carotene-rich foods and after deworming in combination w/ fat suppl. ■ In highly infected children, vegetables and deworming together increased retinol more than vegetables alone.
Christian et al. 1998	Community trial in Nepal; weekly dose of 7000 RE of vit A or β -carotene or placebo	n = 9932 women	<ul style="list-style-type: none"> ■ Incidence of night blindness (XN) during pregnancy was 6.7% in vit A group, 8.9% in β-carotene group, and 10.7% in cont (RR 0.62 for vit A and 0.84 for β-carotene). ■ Incidence of XN in the first 6 mo postpartum was also reduced by 50% to 60% in the vit A group and by 30% to 40% in the β-carotene group.
Manorama et al. 1996	Trial in India; 2.4 μ g/day of β -carotene as sweet snack made w/ red palm oil or 600 IU/day of vit A for 60 days	n = 24; 7 to 9 y old	<ul style="list-style-type: none"> ■ Serum retinol increased from 0.86 to 1.89 μmol/L in the red palm oil group and from 0.74 to 1.94 μmol/L in the vit A group. ■ Results indicate liver saturation w/ vit A to a similar extent in both groups.
de Pee et al. 1995	3.5 μ g of β -carotene as purified β -carotene or as vegetables, 5 days/wk for 12 wk	Pregnant women	<ul style="list-style-type: none"> ■ Purified β-carotene increased serum retinol levels, but β-carotene-rich vegetables had no effect on serum retinol levels.
Bulux et al. 1994	Trial in Guatemala; 6 μ g/day of β -carotene as carrots w/ 10 g of fat or purified β -carotene, or 1000 RE/day of vit A, or placebo for 20 days	n = 67; 7 to 12 y old	<ul style="list-style-type: none"> ■ Serum retinol (34 μg/dL) did not change in all groups. ■ Serum β-carotene level increased almost 3 times in the group receiving purified β-carotene but remained unchanged (13 μg/dL) in all other groups.
Rukmini 1994	700 RE of vit A or red palm oil for 60 days	7 to 9 y old	<ul style="list-style-type: none"> ■ Serum retinol levels increased to the same extent in both groups.
Wadhwa et al. 1994	Trial in India; 2.3 μ g/day of b-carotene in 7- to 9-y-olds and 3.3 μ g/day of b-carotene in 10- to 12-y-olds as carrots, papaya, coriander-mint, or 3 μ g/day of b-carotene as radishes for 1 mo	n = 114; 7 to 12 y old	<ul style="list-style-type: none"> ■ Serum retinol levels after intervention w/ carrots, papaya, and coriander-mint chutney were 25.1 μg/dL. ■ Serum retinol after intervention w/ radishes was 15.5 μg/dL.

Table 8. β -Carotene As a Source of Vitamin A (cont.)

Study	Intervention	Sample	Key findings on β -carotene as a source of vitamin A
Intervention studies			
Carlier et al. 1993	Randomized blind trial in Senegal; treatment w/ β -carotene or vit A for 7 wk	n = 254 (b-carotene); n = 256 (vit A); 2- to 15-y-old children	<ul style="list-style-type: none"> 51.2% of children taking vit A and 50.0% of those taking β-carotene reverted to normal eye cytology after 7 wk of intervention; the two treatments were statistically VAD equivalent.
Hussein and El-Tohamy 1990	Trial in Egypt; different amounts of carrots, carrot juice, or cooked spinach for 2 wk	n = 17; 11- to 13-y-old boys	<ul style="list-style-type: none"> Feeding 150 g/day of carrots increased serum retinol; 30, 50, or 75 g/day did not change serum retinol. Feeding 30 or 45 μg/day of carrot juice did not affect serum retinol or carotene levels. Feeding 150 or 280 g/day of spinach increased serum carotene but not serum retinol.
Hussein and El-Tohamy 1989	Trial in Egypt; 3.7 μ g/day of β -carotene as spinach w/ oil or 2.4 μ g/day of β -carotene as carrots for 40 days, or one dose of 200,000 IU of vit A	n = 13; 6- to 13-y-old boys	<ul style="list-style-type: none"> Serum retinols increased in all three groups from about 17 to 34 μg/dL. Serum carotene increased by 17% in the vit A group and by 42% in the spinach group and was unchanged in the carrot group. β-Carotene-rich foods were as effective as vit A in improving serum retinol levels.
Mariath et al. 1989	Trial in Brazil; 0.8 μ g/day of β -carotene as buriti sweet (made from palm fruit) for 20 days	n = 44; 3 to 12 y old	<ul style="list-style-type: none"> Of the 12 subjects w/ xerophthalmia, 10 showed an improvement; among 31 subjects w/o xerophthalmia, elevated retinol dose-response levels at baseline normalized at follow-up. Vit A status was improved by buriti sweet intake.
Charoenkiatkul et al. 1985	Trial in Thailand; 1.1 μ g/day of β -carotene as cooked ivygod for 2 wk w/ or w/o follow-up suppl w/ 450 RE/day of vit A for an additional 2 wk	n = 30; preschool children	<ul style="list-style-type: none"> Serum retinol increased from 25 to 49 μg/dL and serum β-carotene increased from 27 to 106 μg/dL w/ intake of ivygod w/ no follow-up vit A treatment. In the second group, serum retinol was unchanged during intake of ivygod but increased from 35 to 48 μg/dL during follow-up vit A treatment. β-Carotene-rich vegetables can help maintain vit A status.
Devadas et al. 1980	Trial in India; 1.2 μ g/day of b-carotene as papaya or amaranth, or 300 RE/day off vit A for 2 mo	n = 28; 3 to 5 y old	<ul style="list-style-type: none"> Serum retinol increased from 13 to 29 μg/dL in the papaya group, from 14 to 29 μg/dL in the amaranth group, and from 13 to 35 μg/dL in the vit A group. Hemoglobin levels increased to the same extent in all treatment groups. Papaya and amaranth were equally effective in improving vit A status but less effective than vit A.

Table 8. β -Carotene As a Source of Vitamin A (cont.)

Study	Intervention	Sample	Key findings on β -carotene as a source of vitamin A
Intervention studies			
Jayarajan et al. 1980	Trial in India; 1.2 μ g/day of β -carotene as spinach w/ or w/o oil for 4 wk	n = 70; 2 to 6 y old	<ul style="list-style-type: none"> ■ Serum retinol increased from 20 to 24 μg/dL in the group receiving spinach w/o oil and from 21 to 29 μg/dL in those receiving spinach w/ oil. ■ Effect was most pronounced in subjects w/ initial retinols < 20 μg/dL.
Devadas et al. 1978	Trial in India; 1.2 μ g/day of b-carotene as GLV or purified b-carotene for 2.5 mo	n = 45; 4 to 5 y old	<ul style="list-style-type: none"> ■ Serum retinol increased from 13 to 21 μg/dL in the GLV group and 14 to 22 μg/dL in the purified b-carotene group. ■ GLV were as effective as purified b-carotene in improving vit A status.
Devadas and Murthy 1978	Trial in India; 1.2 μ g/day of β -carotene as amaranth followed by purified β -carotene for 3 mo	n = 15; 3 to 5 y old	<ul style="list-style-type: none"> ■ Serum retinol increased from 21 to 29 μg/dL and hemoglobin increased from 8.4 to 12 g/dL.
Lala and Reddy 1970	Trial in India; 1.2 μ g/day of β -carotene as amaranth for 15 days	n = 29 exp; n = 6 cont; 2 to 6 y old	<ul style="list-style-type: none"> ■ In subjects w/ initial serum retinol of <25 μg/dL, amaranth intake increased serum retinol by 12.6 μg/dL; in subjects w/ initial serum retinol of >25 μg/dL, it was increased by 6.2 μg/dL. ■ β-Carotene through vegetables increased serum retinol.
Pereira and Begum 1968	Trial in India; 1.5 to 2.25 μ g/day of β -carotene as cooked GLV for 3 mo	n = 29; 2 to 5 y old	<ul style="list-style-type: none"> ■ Serum retinol increased from 22 to 31 μg/dL after consumption of GLV.
Lian et al. 1967	1.8 μ g of β -carotene as red palm oil or vit A for 11 to 14 mo; trial in Indonesia	1 to 5 y old	<ul style="list-style-type: none"> ■ Red palm oil improved serum retinol levels.
Roels et al. 1963	7.8 μ g of β -carotene as red palm oil or 600 RE of vit A for 22 days; trial in Indonesia	3 to 13 y old	<ul style="list-style-type: none"> ■ An increase in serum retinol was seen following suppl w/ red palm oil or vit A.
Roels et al. 1958	19 μ g/day of b-carotene as carrots w/ or w/o 1 8 g/day of fat for 31 days; trial in Rwanda	n = 21; 9- to 16-y-old boys	<ul style="list-style-type: none"> ■ Consumption of carrots w/ fat increased serum retinol levels; consumption of carrots w/o fat did not affect serum retinol.

Annex 2. DEFINITIONS OF IMMUNOLOGICAL TERMS

Acute-phase protein response	A predictable set of metabolic reactions to infection or tissue injury characterized by elevations in selected liver-derived proteins (acute-phase proteins), such as C-reactive protein (CRP), α -1 antitrypsin, and α -1 acid glycoprotein.
Antibody	A protein produced normally by specialized B cells after stimulation by an antigen that acts specifically against the antigen in an immune response.
Antigen	A substance that can stimulate an immune response.
B cell	Any of the bone marrow-derived lymphocytes that have antibody molecules on the surface and comprise the antibody-secreting plasma cells when mature; also called B lymphocyte.
Blastogenesis	Transformation of lymphocytes into larger cells that can undergo mitosis.
B lymphocyte	B cell.
CD4	A protein on the surface of helper T cells, which is the receptor for HIV that functions to facilitate recognition of antigens by helper T-cell receptors.
CD8	A protein found on the surface of killer T cells that functions to facilitate recognition of antigens by killer T-cell receptors.
Cell-mediated immunity	The adaptive arm of the immune system in which immunity or the immune response is mediated primarily by T cells, especially killer T cells, rather than by antibodies secreted by B cells (i.e., humoral immunity). Also known as Th1 immunity.
Cytokines	Also known as interleukins (IL). Endogenous mediators derived from leukocytes (white blood cells) and secreted in response to infection or injury. IL-1, IL-6, and tissue necrosis factor are the three cytokines that control the acute-phase protein response.
Delayed-hypersensitivity skin test	A skin test that measures immunity.
Helper T cell	A T cell that participates in an immune response by recognizing a foreign antigen and secreting substances to activate T-cell (Th1) and B-cell (Th2) proliferation, which usually carries CD4 molecular markers on its cell surface, and is reduced to 20% or less of the normal number in AIDS; also called helper cell or helper T lymphocyte.
Humoral immunity	Adaptive immune response that involves antibodies secreted by B cells and circulating in bodily fluids. Also known as antibody-mediated or Th2 immunity.
Immunoglobulin (Ig)	Antibody.

Immunoglobulin A (IgA)	A class of antibodies found in external bodily secretions such as saliva, tears, and sweat.
Immunoglobulin G (IgG)	A class of antibodies including those most commonly circulating in the blood that act against bacteria, viruses, and other foreign proteins.
Immunoglobulin G1 (IgG1)	A subclass of IgG involved in the protective antibody response to tetanus antigens.
Immunoglobulin M (IgM)	A class of antibodies that appear early in the immune response that are replaced later by IgG.
Interferon	Any of a group of antiviral proteins usually produced by cells exposed to the action of a virus and sometimes to the action of bacteria or chemicals.
Interleukin (IL)	Any of various compounds produced by lymphocytes, macrophages, and monocytes that function in regulation of the immune system, especially cell-mediated immunity.
Interleukin 6 (IL-6)	An interleukin produced by various cells, including T cells, that induces maturation of B cells and proliferation of T cells among other functions.
Killer T cell	T cell that usually bears CD8 molecular markers on its surface and that functions in cell-mediated immunity by destroying a cell (such as a tumor cell) having a specific antigenic molecule on its surface; also called killer T lymphocyte, cytotoxic T cell, or cytolytic T cell.
Lactoferrin	Iron-binding protein in the gut.
Lymphocyte	Cells that originate from stem cells and differentiate in the lymphoid tissue (such as of the thymus or bone marrow), which are the cellular elements of the lymph that include the cellular mediators of immunity and make up 20% to 30% of the white blood cells of normal human blood.
Macrophage	A phagocytic tissue cell derived from a monocyte (white blood cell) whose function is to protect the body against infection and noxious substances.
Metallothionein	An intracellular metal-binding protein.
Mitogen	A substance that induces mitosis.
Mitogenic activity/agents	Agents that stimulate or produce mitosis.
Natural killer cell	A lymphocyte capable of killing a tumor or microbial cell without prior exposure to the target cell and without having it presented with or marked by a histocompatibility antigen; also called NK cell.
Phagocyte	A cell that engulfs and consumes foreign material and debris, e.g., white blood cell.
Suppressor T cell	A T cell that suppresses the immune response of B cells and other T cells to an antigen, resulting in tolerance for the antigen; also called suppressor cell or suppressor T lymphocyte.
T4 cell	Any of the T cells that bear the CD4 molecular marker and become severely depleted in AIDS; also called helper-inducer T cell or T4 lymphocyte.

T cell	Any of several lymphocytes that differentiate in the thymus; possesses highly specific cell-surface antigen receptors; also called T lymphocyte.
T lymphocyte	See T cell.

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