

**BENEFITS AND SAFETY OF ADMINISTRATION
OF SYNTHETIC VITAMIN A
TO CHILDREN**

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ACRONYMS

| | |
|--------|--|
| CINI | Child in Need Institute |
| DEVTA | Deworming and Enhanced Vitamin A Trial |
| DPT | Diphtheria, Polio, Tetanus |
| DWCD | Department of Women and Child Development |
| GOUP | Government of Uttar Pradesh |
| HP | Himachal Pradesh |
| ICMR | Indian Council of Medical Research |
| IVACG | International Vitamin A Consultative Group |
| J&K | Jammu & Kashmir |
| KGMC | King George Medical College, Lucknow |
| MI | Micronutrient Initiative |
| MOHFW | Ministry of Health and Family Welfare |
| MP | Madhya Pradesh |
| NEI | National Eye Institute |
| NFHS | National Family Health Survey |
| NFI | Nutrition Foundation of India |
| NGO | Non-government Organization |
| NIDS | National Immunization Days |
| NIN | National Institute of Nutrition |
| NNMB | National Nutrition Monitoring Bureau |
| OPV | Oral Polio Vaccine |
| ORS | Oral Rehydration Solution |
| PHC | Primary Health Care |
| RDA | Recommended Daily Allowance |
| UNICEF | United Nations International Children's Emergency Fund |
| UP | Uttar Pradesh |
| USAID | United States Agency for International Development |
| VAD | Vitamin A deficiency |
| WHO | World Health Organization |

BENEFITS AND SAFETY OF ADMINISTRATION OF SYNTHETIC VITAMIN A TO CHILDREN

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ABSTRACT

This paper describes the benefits and safety of vitamin A administration to children. A review of the literature is presented on the clinical and sub-clinical profile of vitamin A deficiency (VAD) in India, and the efficacy/effectiveness of supplementation relative to infant and child mortality and morbidity worldwide. The paper also reviews safety and toxicity issues as well as the logistics and cost-benefits of vitamin A supplementation. The paper concludes clinical vitamin A deficiency is prevalent in India, albeit variations in the proportion of children affected varies among and within States. Data on sub-clinical VAD is limited. However, existing data suggest prevalence is substantial and more widespread than reported. If WHO standards for clinical and sub-clinical VAD are applied, VAD constitutes a public health problem in India. The paper further concludes vitamin A sufficiency reduces general mortality in children less than 60 months of age who previously exhibited clinical or sub-clinical deficiency. It is agreed that vitamin A sufficiency likely reduces mortality from measles in VAD children, but the impact of vitamin A on morbidity from diarrhea, respiratory disease, malaria or tuberculosis is uncertain. It is suggested vitamin A distribution programs have proven effectiveness in improving retinol levels and reducing general mortality in vitamin A stressed children less than 60 months of age. The paper concludes vitamin A is a safe, cost effective child survival intervention whose benefits outweigh the risks, particularly where clinical and sub-clinical deficiency are prevalent. It is recommended children 6-60 months be universally supplemented with an appropriate dose of vitamin A, and VAD be prevented over the long term through supplementation and improved dietary intake.

BENEFITS AND SAFETY OF ADMINISTRATION OF VITAMIN A TO CHILDREN

I. Introduction

Recent research in a number of countries around the world suggests that increased intake of vitamin A in environments with a high prevalence of sub-clinical vitamin A deficiency reduces child mortality and the severity of some common infectious diseases in children. Decision-makers in many countries have elected to act on that evidence to incorporate specific activities into health programs to increase the vitamin A intake of children. These programs include:

- direct supplementation with vitamin A;
- fortification of both staple and luxury foods with vitamin A and;
- increase supply and consumption of vitamin A rich foods by children.

The decision regarding the appropriate choice of a program option or a mix of options, the allocation of resources among these interventions is complex. The direct and indirect costs, as well as the benefits of each approach, are difficult to measure. However, scientific answers to the following questions provide a rationale for such decisions.

- 1) Does the level of clinical or sub-clinical vitamin A deficiency in the population constitute a public health problem?
- 2) If yes, have any public health interventions for the delivery of vitamin A proven to be efficacious¹ in populations with characteristics similar to those of the target population?
- 3) From among available interventions, which are feasible and cost-effective given the existing infrastructure?
- 4) Are there known risks, such as toxicity, or other negative attributes of cost-effective interventions?
- 5) Within the context of the larger health program, are there valid reasons for selecting one approach or a combination of approaches?

This paper provides data from around the world as well as in India to shed light on the answers to these questions, especially regarding the administration of synthetic vitamin A supplements.

This paper limits the discussion of vitamin A supplementation to apparently healthy children who may have subclinical conditions of deficiency and infection.

II. VAD Status in India

Data on prevalence of clinical signs, sub-clinical deficiency and dietary intakes have been used to draw conclusions on the prevalence of vitamin A status in India.

¹ i.e. in reducing mortality and disease severity

A. Clinical Profile of VAD in India:

WHO's "Micronutrient deficiency Information System" lists India as one of 60 countries with a VAD level of public health significance (WHO, 1995). More recent data on the prevalence of vitamin A deficiency indicate that VAD continues to be a public health problem.

Data from five districts in Assam, Bihar, UP, HP and J&K indicate that the prevalence of Bitot Spots is **1.84%** (range 0.04%-4.75%) and Night Blindness is **1.84%** (range 0.04%-4.85%) in children under 6 years of age (ICMR District Nutrition project, 2000). WHO cut-offs for a public health problem are 0.5% for Bitot's spot and 1.0% for night blindness

A KGMC/UNICEF/GOUP study in Bhabraich district of UP found Bitot's spot incidence to be **5.6%** and Night Blindness incidence to be **3.4%** with wide variation from cluster to cluster (KGMC/UNICEF/Government of UP Report on Vitamin A deficiency in Bhabraich district - under preparation). The lower incidence of night blindness was attributed to the dosage of vitamin A administered in the district in the preceding 6 months and to the exclusion of children 6 -24 months.

Data from eight states surveyed by the NNMB is presented in Table 1 (NNMB, 1996).

Table 1: Bitot Spot Prevalence & Estimated Dietary intake of Vit. A, NNMB Report 1996

| State | 1-5 yrs (Boys & Girls) | 5-12 yrs (Boys & Girls) | Estimated Dietary intake, CU/day (μg) |
|----------------|---------------------------|----------------------------|---|
| Kerala | - | 0.5 | 214 |
| Tamilnadu | 0.8 | 6.3 | 184 |
| Karnataka | 0.4 | 2.9 | 286 |
| Andhra Pradesh | - | 2.2 | 352 |
| Maharashtra | 1.5 | 1.6 | 222 |
| Gujarat | - | 1.3 | 263 |
| Madhya Pradesh | 5.6 | 5.9 | 343 |
| Orissa | 0.4 | 1.9 | 436 |
| Pooled | 1.1 | 2.8 | 288 |

Figures in bold represent values above the WHO cut off point (0.5%); RDA - 600 μg per day

The data indicate the prevalence of clinical VAD in children <13 years is significant and the dietary consumption of vitamin A is only about 50% of RDA (288/600 μg). These results argue for regular periodic tracking of prevalence, severity and clinical VAD in Indian children.

Table 2 presents data from a survey of eighteen States/Union Territories on ocular signs and maternal night blindness (DWCD, 1998 and NFHS-2, 2000).²

Table 2: Prevalence of clinical vitamin A deficiency (DWCD, 1998 & NFHS-2, 2000)

| State/UT | Ocular Signs - DWCD, 1998 | | | | Maternal Night Blindness NFHS-2, 2000 |
|---------------------------------------|---------------------------|-------------------|------------------|-------------------|---------------------------------------|
| | Bitot's Spot (%) | Corneal Xerosis % | Kerato-malacia % | Corneal Opacity % | |
| Delhi | 0.05 | 0.02 | 0.039 | 0.003 | 3.8 |
| Haryana | 0.04 | 0.01 | 0 | 0 | 1 |
| Himachal Pradesh | 0.01 | 0 | 0 | 0 | 3.8 |
| Chandigarh | 0 | 0 | 0 | 0 | |
| Jammu | | | | | 18.5 |
| Punjab | 0.12 | 0 | 0.01 | 0 | 0.8 |
| Rajasthan | 0.22 | 0.16 | 0.09 | 0.02 | 14.7 |
| Madhya Pradesh | 2.62 | 0 | 0 | 0 | 19.7 |
| Uttar Pradesh | | | | | 14 |
| Bihar | 0.14 | 0.08 | 0.06 | 0.06 | 19.4 |
| Orissa | 0.86 | 0 | 0 | 0 | 18.7 |
| West Bengal | | | | | 11.6 |
| Arunachal Pradesh | 0.34 | 0.36 | 0.24 | 0.25 | 20.2 |
| Assam | 0.45 | 0 | 0 | 0 | 6.9 |
| Manipur | 0.14 | 0.08 | 0.15 | 0.12 | 8.5 |
| Meghalaya | 0.18 | 0.07 | 0.11 | 0.1 | 23.9 |
| Mizoram | 2.97 | 1.27 | 0.28 | 0.69 | 14.6 |
| Nagaland | 0.35 | 0.32 | 0 | 0.07 | 21.1 |
| Sikkim | 0.19 | 0.86 | 0.01 | 0.07 | 21.6 |
| Goa | 0 | 0.1 | 0 | 0 | 2.2 |
| Gujarat | 0.20 | 0 | 0 | 0 | 10.9 |
| Maharashtra | 0.72 | 0 | 0 | 0 | 9.7 |
| Andhra Pradesh | 0.79 | 0 | 0 | 0 | 5.3 |
| Dadra Nagar Haveli | 0.38 | 0 | 0.11 | 0 | |
| Daman & Diu | 0 | 0 | 0 | 0.05 | |
| Karnataka | 0.77 | 0 | 0 | 0 | 6.3 |
| Kerala | 0.25 | 0 | 0 | 0 | 2.1 |
| Tamil Nadu | 3.11 | 0 | 0 | 0 | 3.7 |
| Tripura | 0.02 | 0.12 | 0.04 | 0.03 | |
| WHO cut off for public health problem | >0.5% | >.01%* | | | Do not exist |

Figures in bold represent values above the WHO cut off point for the category.

*The WHO cut off for Corneal Xerosis and/or Corneal ulceration is 0.01% (corneal Xerosis + Keratomalaria + and Corneal Opacity). The data in this table are segregated and thus may underestimate the prevalence of VAD-related ocular disease.

² Information on training and experience of assessors; inter-assessor variability; season; and recent vitamin A supplementation for the data in Table 1 & 2 is not known.

These data further suggest the need for a tracking system to monitor the prevalence of VAD. Furthermore, the prevalence of night blindness in pregnant women appears high in some states. Although standards for defining VAD as a public health problem for pregnant women are unavailable, double-digit rates of night blindness in pregnant women almost surely indicate widespread deficiency.

A study of the pattern and distribution of ocular morbidity in primary school children in rural Delhi showed that vitamin A deficiency related ocular disease was the second most common symptom (10.6% of children) after trachoma (18%) (Chaturvedi and Aggarwal 1999). Khandait reported an overall prevalence of xerophthalmia of 8.7% in children under 6 years in urban slums of Nagpur. The prevalence of xerophthalmia, as well as subclinical vitamin A deficiency was higher in children over 3 years old than in under 3 years of age (Khandait et al. 1999).

All available data indicates VAD to be a significant public health problem. Dietary intake of vitamin A is only about 50% of the RDA, therefore a widespread vitamin A deficiency can be expected. Despite a vitamin A distribution program in place, VAD levels are high. Prevalence of ocular signs, which are rare events and occur only in severe VAD, is above the WHO cutoffs in most states of the country. Maternal night blindness rates are high in several states. There is wide variation in prevalence of VAD from cluster to cluster within a district (Bharaich district study). This has important implications for public health i.e. a district/state targeted approach is not appropriate for vitamin A administration but national universal coverage of children is essential to reach all deficient children.

B. Sub-clinical Profile of VAD in India:

Systematic population-based estimates of sub-clinical vitamin A deficiency are not available. Clinical signs of vitamin A deficiency emerge in extreme cases of deprivation; and high levels of sub-clinical deficiency are found frequently in populations with little or no observable clinical disease. The low dietary intake of vitamin A (less than 50% - Table 1) are almost surely indicative of widespread sub-clinical deficiency. Based on prevalence data reported from small studies, the international community estimated the sub-clinical prevalence rate to be 18% in 1995. (MI/UNICEF/Tulane University 1998).

Preliminary data from the DEVTA study from five districts in Uttar Pradesh (Hardoi, Sitapur, Raibareilly, Unnao and Kheeri) suggest sub-clinical vitamin A deficiency ranges from 34% to 56% in children < 60 months. According to international standards, proportions above 20% are indicative of a public health problem.

Available sub-clinical data, though limited, indicates that a high prevalence of subclinical deficiency may exist. In conclusion clinical VAD may remain prevalent in certain areas of India and in specific cohorts of at-risk populations. The need is to survey VAD. An appropriate system that tracks VAD in a periodic, easy, accurate, rapid and relatively inexpensive manner should be considered for institutionalization as part of the vitamin A program.

III. Efficacy of Vitamin A Supplementation

Efficacy is the power or capacity to produce desired effects in a controlled setting. As understanding of the biological importance of vitamin A has grown, public health practitioners have attempted to verify the anticipated effect of vitamin A on morbidity and/or mortality in children through a series of efficacy studies (Beaton and McCabe, 2000)³.

A. Infant and child mortality

A strong link between vitamin A deficiency and increased mortality in humans was first described by Sommer in the early 1980s (Sommer et al, 1983 and 1996). Additional studies in Asia and Africa, including two in India, to determine whether or not the observations from Indonesia were conducted to verify these findings.

The attached document "Report of a Joint WHO/USAID/NEI Consultation of Principal Investigators of vitamin A Mortality and Morbidity Studies" presents a summary of the main studies. Principal Investigators agreed that in areas where vitamin A deficiency is of public health importance, vitamin A sufficiency reduces mortality in children 6-60 months of age. They also agreed that variations among communities and regions may influence the extent of impact.

The "community-based research" led to three meta-analyses by Beaton et al. (1993), Fawzi et al. (1993), and Glasziou and Mackerras (1993). These analyses present a clear consensus that improving vitamin A intake reduces childhood mortality in vitamin A deficient children.⁴ Key findings are presented below:

- Vitamin A can reduce all-cause mortality **23%, 30% and 30% respectively** in children 6-60 months of age
- All three meta-analyses highlighted the importance of vitamin A in reducing mortality resulting from measles and diarrhea.

³ Scrimshaw et al. 1968, in a comprehensive review of interactions between nutrients and infections concluded that vitamin A deficiency showed synergism with almost every known infectious disease (Scrimshaw et al. 1968). The probable mechanism by which vitamin A deficiency increases the risk of mortality is through reducing the immune response to infection. Incidence and duration of infection may not be altered but severity is (Beaton et al. 1993).

Intensive investigations over the last two decades have helped unravel the complex roles of vitamin A in the molecular functioning of the immune system although the precise role of vitamin A in maintaining immunocompetence is yet to be understood. It is known that vitamin A plays a critical role in maintaining lymphocyte function; it functions in T cell-mediated responses; there is reasonably good evidence that vitamin A can stimulate nonspecific immunity, such as the activation of macrophages; and, the importance of retinoic acid in gene expression has been described (Ross, 1996).

⁴ The studies by Beaton et al. and Fawzi et al. included eight studies, while Glasziou and Mackerras included five studies.

- The relative effectiveness of vitamin A supplementation is neither gender dependent nor age dependent in children 6 to 59 months of age. However, since the absolute number of deaths in children is greatest in young children (6-24 months of age), increased vitamin A intake among that age group will have the greatest impact on the number of children dying in areas where vitamin A deficiency is a public health problem.⁵

It should be noted that these meta-analyses do not address deficiency in infants under 6 months of age. Second, they were all done in settings with a moderate to high degree of clinical and subclinical VAD. Abdeljaber et al. 1991 and Rahmathullah et al. 1991 showed a protective effect on mortality and no impact on morbidity of respiratory illness or diarrheal diseases. One possible explanation could be that vitamin A supplementation may only reduce the severity, but not the incidence of infection as seen in the study from Ghana (Arthur et al. 1992).

The published evidence shows that vitamin A supplementation lowers child mortality in vitamin A deficient children, 6-60 months of age. The beneficial effects of vitamin A supplementation are similar in both girls and boys between the ages of 6 months and 5 years. Measles-related mortality is reduced as is mortality attributed to severe diarrhea.

B. Infant and child morbidity

The impact of vitamin A on childhood morbidity is unclear. There is no consistency in results from investigations on the effect of supplementation with vitamin A in improving morbidity symptoms. Some evidence indicates that improvement in vitamin A status impacts upon the progression of illness to its severe forms, and to its severest form, mortality” (Beaton et al. 1993).

Measles: The strongest evidence that improving vitamin A intake reduces the severity of illness relates to measles. The meta-analyses of Fawzi et al. (1993) and Glasziou and Mackerras (1993) reported mortality reductions from vitamin A supplementation of 63% and 66% respectively for patients hospitalized with measles. Reductions in mortality attributed to measles and diarrhea from community-based trials were reported by all three meta-analyses.

Diarrhea: The results from community-based studies relating to incidence and prevalence of diarrheal morbidity are inconsistent. Studies by Bhandari et al. (1997), En-Lin et al. (1995), Lie et al. (1993) and Barreto et al. (1994), Bloem et al. (1990), Ross et al. (1995) and Coutoudis (1995) show benefits of vitamin A supplementation in severe diarrhea. Studies by Abdeljaber et al. (1991), Vijayaraghavan et al. (1990), Dibley et al. (1996), Ramakrishnan et al (1995), Rahmathullah et al. (1991), and Sinha et al. (1976) showed no impact of vitamin A supplementation on diarrheal morbidity. One study, Stansfield et al. (1993) reported an increase in risk of diarrhea.

⁵ *Beaton et al. (1993) emphasized that the beneficial role of vitamin A in young child mortality was biological, rather than pharmacological. That is, it was not dependent on the administration of periodic high potency doses of vitamin A. Rather it was related to an improvement of vitamin A status by any effective means.*

Respiratory illness: The Vitamin A and Pneumonia Working Group (WHO, 1995) undertook a meta-analysis of data from 12 studies and concluded that supplementation had no significant effect on the incidence of, or mortality from pneumonia. Some studies have shown benefits from a standard high dose vitamin A supplementation (Pinnock et al. 1986, Pandey et al. 1991, En-Lin et al 1995, Lie et al. 1993, Bloem et al. 1990); other studies found no effect (Ramakrishnan et al. 1995, Vijayaraghavan 1990, Barreto et al. 1994, Rahmathullah 1991); and, two studies have described a harmful effect in well-nourished children (Dibley et al. 1996, Stansfield et al. 1993).

Overall morbidity: Arthur et al. (1992) found that 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. They also found that the mean daily prevalence of vomiting was lowered by 13% by 4-monthly high dose vitamin A supplementation for 1 year in Ghana. Conversely, Donnen et al. (1998 b) found no effect of high-dose vitamin A supplementation or deworming on common morbidity of diarrhea, cough, cold, or fever in malnourished preschool children. Thus, the effect of vitamin A supplementation on overall morbidity is not known.

Malaria and Tuberculosis: Some studies suggest possible associations with malaria (Tabone et al. 1992, Galan et al. 1990, Shankar et al 1999) and tuberculosis (Smurova and Prokop'ev 1969, Covacev and Salomone 1966, Paul and Vidya, 1999) but more studies are needed to study the effect of vitamin A deficiency, and subsequent vitamin A supplementation, on the incidence, severity, and mortality from malaria and tuberculosis.

The effect of vitamin A supplementation in improving general morbidity symptoms is not known. Supplementation with vitamin A reduces the severity of measles. It is unclear whether vitamin A supplementation significantly reduces the incidence or duration of diarrheal morbidity. Prophylactic vitamin A supplementation does not have any benefit on the incidence or mortality from pneumonia. More studies are needed to show the effect of vitamin A deficiency on malaria and tuberculosis.

IV. Effectiveness of vitamin A supplementation

Effectiveness is the ability to produce a desired effect under conditions of expected usage (Beaton and McCabe, 2000). The literature addressing effectiveness in terms of mortality reduction in children of large-scale vitamin A programs through increased intake of vitamin A, either natural or synthetic is virtually non-existent. However, given proven efficacy and the high expense of measuring mortality in large scale programs, vitamin A coverage is an accepted proxy for effectiveness.

There are now a number of examples of programs that have reached high level of coverage fairly quickly in difficult environments. These programs rely on the periodic distribution of synthetic vitamin A in the form of capsules or syrup. Nepal has instituted a national coverage program in 1994 which has achieved remarkable coverage (UNICEF/WHO/MI/GON, 1998).

As noted in the introduction, supplementation is but one of a number of options for increasing vitamin A intake in children and mothers. The effectiveness of fortification of sugar with

vitamin A was demonstrated in Guatemala through a series of surveys measuring the prevalence of inadequate retinol in children and in the breast milk of nursing mothers. During the first year of sugar fortification, the proportion of children under 5 years of age with inadequate retinol decreased from 21.5% to 5.1% (Arroyave, 1979). When sugar fortification was halted, the prevalence of vitamin A deficiency increased again (Mora et al. 2000).

A recent literature review of food-based strategies other than fortification concluded that little has been done to rigorously evaluate the efficacy or effectiveness of food-based programs (Ruel and Levin, 2000). A comparison of the effectiveness of supplementation, fortification and dietary change is not possible at this time.

In the past 12 months, programs have been initiated with USAID funding in Zambia and Ghana that have achieved approximately 70% coverage on a national basis by the second round of distribution. These programs were built upon vitamin A distribution through NIDS, but are now established institutionalized programs independent of NIDS. As these programs are so new, results are not yet available.

V. Safety and Toxicity Issues

Safety: The risks of harm from a single age-appropriate high dose of vitamin A are small. The high levels of retinol esters present after dosing are cleared quickly from the blood; and, once stored, vitamin A is harmless. For children, a single high dose, appropriate for age, will not harm anyone and may help many. Side effects, particularly bulging fontanel, sometimes occur, but these are mild and transient. Iliff et al. (1999) investigated tolerance of large doses of vitamin A given to mothers and their babies shortly after delivery. In a randomized, double blind trial, mothers received 400,000 IU and acute symptoms did not differ between the treatment and control groups. In the babies who received 50,000 IU, they found the incident rate of bulging fontanel on examination was 1.5%, not significantly different from the 1.0% observed in the control groups (p=0.5).

Toxicity: The exact level of consumption at which young children exhibit toxicity symptoms is difficult to determine as several factors influence the toxicity threshold. Among these are the size and age of the individual, the duration of consumption, and the quantity and form of vitamin A consumed. Olson (1996) determined that for children the threshold for acute toxicity was a single dose of >330,000 IU. The 1997 guidelines of WHO/UNICEF/IVACG state that "...if a high-dose supplement has been administered more than one month previously, an additional dose is not harmful. In contrast, a child who has received a routine high-dose supplement within the past month should not receive an additional targeted dose." (WHO/UNICEF/IVACG 1997, page 5)

Safety and Efficacy of Concurrent Vitamin A Supplementation and Immunization: Linking the distribution of vitamin A supplements with administration of immunizations is an efficient way of utilizing scarce public health resources. However, it is important to be sure that the vitamin A will not interfere with the efficacy of the immunizations or that administering both interventions concurrently will be feasible from an operational point of view. These questions have been addressed comprehensively and the results confirm the rationale for integrating the two interventions.

The effect of vitamin A administration on the seroconversion of DPT and OPV vaccines has been investigated and shown not to interfere with the efficacy of DPT or polio vaccines. Rahman et al. (1999) showed that a vitamin A supplement at the time of DPT immunization resulted in an increased antibody response to diphtheria compared to that of non-supplemented infants. The antibody responses to pertussis and tetanus vaccines, however, were not affected by vitamin A administration. A study by Semba et al. (1999) infants receiving vitamin A with trivalent oral polio vaccine at 6, 10, and 14 weeks of age the vitamin A supplementation had no effect on antibody responses to poliovirus types 1, 2, and 3 at enrollment or at 9 months of age.

The results of five controlled intervention studies investigating the effect of vitamin A on the efficacy of measles vaccine (Semba et al. 1995, 1997; Stabell-Benn et al. 1995, 1997; Bahl et al. 1999) allow a definitive conclusion 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).

A recent WHO sponsored multi-center randomized trial in over 9,000 children assessed the benefits and safety of three doses of 25,000 IU vitamin A supplementation linked to DPT/OPV immunization at 6, 10, and 14 weeks following postpartum vitamin A supplementation. Although bulging fontanelles were observed within 48 hours of administration in a higher proportion of the supplemented group than the observation group, less than 1% of either group were affected. The regimen used in this trial had no effect on observed vitamin A status at age 9 and 12 months but, at 6 months, vitamin A status of the supplemented group was better than the (WHO/CHD, 1998). This trial confirmed the safety of the intervention.

A recent evaluation of the safety and feasibility of administering high-dose vitamin A supplements with oral polio vaccine (OPV) as part of the Intensified Pulse Polio Immunization Campaign in the State of Orissa, India (State Government of Orissa/WHO/NIN, 2000) showed that of the 879 children randomly selected for the study (97% reportedly received OPV) 73% of children received a dose of vitamin A; coverage was 21% among infants under 12 months old (who were later determined to be all above 9 months of age), 92% among children 12-42 months old, and 49% among those older than 42 months. The incidence of illness (vomiting, fever, diarrhea, nausea, excessive crying, or others) within 48 hours of administration was similar in children who received OPV and vitamin A (3.0%), OPV alone (2.8%), or neither OPV nor vitamin A (3.8%). Similar results were seen in infants. Bulging anterior fontanelle was observed in one child who was 13 months old. Although the target group for vitamin A administration was children 12-42 months old, infants <12 months old and children >42 months old also received vitamin A. The results of this safety study, which was a part of a larger comprehensive evaluation including biological impact, indicate that it is feasible to provide vitamin A along with OPV with high coverage and tolerance in children. There is, however, a need to improve the knowledge and adherence to protocol by vaccinators.

VI. Economic and Logistic issues

A. Economic considerations

There is a strong economic rationale for investing in micronutrient programs. In a World Bank assessment Levin et al. 1993 concluded that, due largely to the potential magnitude of vitamin A impacts on infant and child mortality, the number of productive years gained per dollar invested for vitamin A supplementation ranked favorably with other known mortality reduction technologies. In another comprehensive study in the Philippines universal supplementation with vitamin A every six months yielded benefits of 2.4 to 3.4 times the costs of the program (Popkin et al. 1980). This study was undertaken before the full mortality impact of vitamin A was appreciated and thus it can be anticipated that this benefit ratio would be even larger at this time if the study were to be repeated.

In India, the current cost of supplementing a child with age-appropriate dose every six months up to the age of five is Rs 8.50, which is less than the cost of a liter of milk (MOHFW information: cost of 100 ml bottle is Rs 50, each ml contains 100,000 IU vitamin A). Since the supplements are delivered through the existing Primary Health Care system, additional costs are expected to be modest. Nationally, an investment of Rs 180 million annually in vitamin A supplements could potentially save the lives of 1-1.4 million children. Cost-benefit ratios of other approaches are not available, but will predictably be much higher.

B. Logistic issues: production, supply, coverage and models for distribution

Production and supply: Vitamin A is manufactured in-country by a national pharmaceutical company, Nicholas Piramal India Ltd, who bought the production plant from Roche Products Ltd. in 1993. The vitamin A produced as retinol palmitate and acetate is currently produced from Pseudo-Ionone. This is imported since the lemon grass oil, earlier available from Kerala, is no more available as the farmers have switched to rubber plantations. The production capacity is enough to meet requirements (current capacity of the Piramal plant is 160 tons/160 million million units of vitamin A of 1.0 million IU/gm). Bulk prices are fixed by National Pharmaceutical Pricing Authority (letter of 8/22/2000 by Dr. R. Krishna, Vice President - Marketing, Nicholas Piramal India Ltd.)

Pharmaceutical companies purchase the bulk vitamin A for further formulations including for supplying to the national program. Vitamin A is distributed in Kit A, which contains 6 bottles of 100 mL vitamin A solution (100,000 IU/mL). Two such kits are supplied per sub-center.

The NFI (1998) conducted a comprehensive situational analysis of the supply and demand of micronutrient and micronutrient-related supplements in 2 districts of MP and a similar study was conducted by CINI (1998) at the state level for West Bengal. Supply, logistics, quality and coverage constraints identified by these studies included:

- The budget allocated to the Micronutrient Prophylaxis Program depends on the total budget that the Planning Commission allocates to the Ministry of Health and Family Welfare.

- The vitamin A syrup provided to the sub-health centers falls very short of meeting the quantities requirements. The quantities per kit should be raised in proportion to beneficiaries served.
- The supply of vitamin A oil is irregular at all levels – State, District, PHC, and sub-health center levels. State-District communication regarding supplies is poor resulting in coordination difficulties. Regular and timely supplies based on regular reports of requirements must be ensured.
- Proper supervision and monitoring of stores is needed at all levels. The physical facilities of the stores were inadequate. Store keepers and officers need to periodically undergo a service training program in logistics management.
- The quality of vitamin A syrup is monitored by government-approved laboratories at the national level before dispatch to the States and Union Territories. At least one quality control laboratory must be established in each State capital to ensure the quality of micronutrients and drugs at the State and lower levels.

Coverage: In 1996, the MOHFW estimated that vitamin A coverage for children 6-11 months old was 68% while that for children 1-5 years old was 25%. An NFI (1999) study in MP found that 28% of children had ever received vitamin A syrup.

The most comprehensive and recent coverage data presented in Table 3 (NHFS, 2000 - under publication) shows that coverage with vitamin A supplements is low - only 30% children have received a dose of vitamin A and about 17% received a dose in the 6 months preceding the survey. **This implies that coverage through routine services is not reaching levels at which the full benefit of mortality reduction through vitamin A coverage may be achieved.**

While clear, positive impacts can result from a strategy of integrating vitamin A supplementation into routine health services, it is important to recognize that this approach focuses on children within the first year of life. Once children have been immunized, they are likely to come back for services only when they are sick. What is needed is a mechanism that will continue coverage during the critical years of childhood. **An active approach that seeks out the largest number of children in the target group is necessary** to achieve the levels of population coverage required to realize the full potential of vitamin A supplementation in reducing child mortality.

Table 3: Percentage of Children Age 12–35 Months who Received at least One Dose of Vitamin A and Who Received at least One Dose of Vitamin A Within the Six Months Preceding the Survey by State, India, 1998–99

| State | Percentage who received Vitamin A | |
|-------------------|-----------------------------------|-----------------------------------|
| | At least on dose | One dose within the past 6 months |
| INDIA | 29.7 | 17.1 |
| North | | |
| Delhi | 32.7 | 17.4 |
| Haryana | 45.2 | 21.4 |
| Himachal Pradesh | 71.1 | 35.1 |
| Jammu | 36.0 | 22.8 |
| Punjab | 56.5 | 30.2 |
| Rajasthan | 17.6 | 12.5 |
| Central | | |
| Madhya Pradesh | 24.4 | 14.7 |
| Uttar Pradesh | 13.9 | 9.5 |
| East | | |
| Bihar | 10.2 | 6.8 |
| Orissa | 42.0 | 26.4 |
| West Bengal | 43.4 | 23.5 |
| Arunachal Pradesh | 20.9 | 9.6 |
| Assam | 15.4 | 8.9 |
| Manipur | 38.4 | 18.8 |
| Meghalaya | 24.7 | 10.7 |
| Mizoram | 70.6 | 41.8 |
| Nagaland | 6.8 | 4.4 |
| Sikkim | 45.8 | 22.0 |
| West | | |
| Goa | 78 | 52.3 |
| Gujarat | 51.9 | 26.3 |
| South | | |
| Maharashtra | 64.7 | 36.6 |
| Andhra Pradesh | 24.8 | 14.0 |
| Karnataka | 48.4 | 22.8 |
| Kerala | 43.6 | 28.2 |
| Tamil Nadu | 16.2 | 10.0 |

Note: Table includes only surviving children from among the two most recent births in the three years preceding the survey.

Source: NFHS-2, 2000

Models for distribution: Three active outreach-type strategies have been developed to achieve high vitamin A coverage: Child Health Weeks, Micronutrient Days, and Community-Based Outreach. Although these three strategies are described separately, there is an enormous

potential for overlapping benefits. Approaches for active vitamin A outreach strategies usually share four principles:

- They are periodic (usually twice a year) either during a specified week or day(s);
- They are "active" in that mothers are asked to take their child to designated centers, outreach posts for delivery of the supplements;
- They are institutionalized in that it is run or managed routinely by health workers; and,
- They are often integrated with other interventions such as growth promotion, deworming, bed nets, vaccinations, and other micronutrients.

In Child Health Weeks, vitamin A supplements have been incorporated into a package of preventive services designed to improve child survival. By establishing a semiannual cycle of district activities designed to improve facility usage for preventive services, coverage of several key child survival interventions may be improved. This approach works well in decentralized health systems where district-level health staff develop a strong sense of ownership of the intervention.

This model has worked well in Nicaragua, where, since 1994, twice-yearly integrated National Health Rallies have included vitamin A supplements, ORS, de-worming, growth monitoring, iron supplements, and routine immunization. This has resulted in vitamin A coverage above 70 percent, the highest in all of Latin America. The services are provided at health facilities, and the rallies may last several weeks. Public and professional recognition encourages health staff to achieve high rates of coverage. Communities are mobilized by engaging media, churches, and other community groups

This approach is also being used with success in Zambia where vitamin A provided the foundation of the preventive package. Health center district managers view this as an opportunity to upgrade coverage on numerous preventive health interventions. The objectives of the Child Survival Promotion Week in February 2000 addressed vitamin A supplement coverage, routine vaccination coverage (particularly nine-month measles), helminth infections, and growth promotion. This strategy presents an opportunity to promote other health education messages, including exclusive breast-feeding, postnatal vitamin A and iron needs, and use of treated bed nets for malaria.

Niger and the Philippines provide examples of Micronutrient Days, programs where specific dates during the year were identified as the focus for distributing vitamin A supplements and other micronutrients such as iron and folic acid tablets. These may be either national or sub-national, but they are distinguished by focusing efforts on micronutrients rather than on a range of preventive activities. The fourth Philippines National Micronutrient Day was undertaken in 1996 and coverage with vitamin A was estimated at 90%. This contrasts with coverage of less than 10% achieved through reliance on routine health services prior to 1993 when NIDs and Micronutrient Days were introduced. Micronutrient Days in the Philippines have been more recently expanded to include other preventive health services and it is now called Guaranteed Health for Children.

The best example of community-based outreach is the Nepal program. Female community health volunteers distribute supplements on the same four days every year (two days for the first distribution and two for the second). The program has expanded progressively and in 2001 all 75 districts in Nepal will be participating. The investment in the new districts added to the program in a given year is quite high as there is a need for promotion, training, mobilization, and monitoring and evaluation. After that first year, however, the program is left in the hands of local authorities and, impressively to date, there has been no measurable drop in coverage, even in the districts that joined the program as early as 1993. The success of the program is attributed to the pride of ownership in the program established by the cadre of female community health volunteers. Another critical success factor is the leadership and management expertise of the local technical assistance group (an NGO). Mini-surveys are used to measure coverage and provide feedback

VII. Conclusions and Recommendations

A. Conclusions: The scientific evidence presented earlier clearly shows that:

Clinical vitamin A deficiency in India is prevalent in children up to six years of age as well as in older children, perhaps higher than previously thought. Per internationally accepted standards, the deficiency levels indicate a problem of public health significance. Though sub-clinical deficiency prevalence has not been assessed systematically, dietary intake data and the limited data on subclinical deficiency indicate a high incidence of sub-clinical deficiency. The magnitude of clinical and sub-clinical VAD needs to be addressed through a rapid public health intervention to improve the vitamin A status of the large numbers of children suffering from VAD. This is essential until such time that improvements in diets can ensure adequate vitamin A intake.

The efficacy of reducing mortality in vitamin A stressed children, 6-60 months of age, through adequate vitamin A intake (regardless of the form of delivery) has been well established.

Supplementation of children with mega doses (appropriate for age) every six months has been shown to be an efficacious, easy, simple and cost-effective form of improving vitamin A intake. Benefits heavily outweigh the risks.

Administering six-monthly vitamin A to children is an ongoing intervention in the country and the necessary infrastructure for its delivery exists throughout the country. The vitamin A is produced in-country, with adequate capacity to meet the public health program requirements and price regulation by the government. Thus, the basic requirements for a sustainable public health intervention exist.

There is wide variation in incidence of VAD from cluster to cluster within a district (Bharaich district study), thus a district/state profile is not appropriate for prioritizing areas for vitamin A administration. National universal coverage of children is essential to reach pockets of clinically and sub-clinically vitamin A deficient children within a state/district.

The current coverage of the vitamin A program is low and needs improvement. Constraints that have limited coverage are resource allocations, supply and logistic issues, low priority and the lack of actively seeking out children for supplementation.

Experience from several countries shows that routine, periodic, active, institutionalized delivery models integrated with other preventive services have successfully improved coverage.

B. Recommendations:

Children between 6 months and five years of age must be universally supplemented with the prescribed dose of vitamin A every six months (100,000 IU at 9 months and 200,000 IU subsequently). To achieve this the following is recommended:

1. Consider expanding the current policy to include coverage of children 6 - 60 months of age, with appropriate resource allocation.
2. Consider adopting active, institutionalized distribution of vitamin A supplements through six-monthly nutrition days/weeks. These could serve as effective mechanisms for disseminating appropriate messages on combating VAD through supplementation and improving diets.
3. Consider institutionalizing a system to monitor the prevalence of clinical and sub-clinical VAD.

IX. References

Abdeljaber MH, Monto AS, Tilden RL, Schork MA, Tarwotjo I (1991) The impact of vitamin A supplementation on morbidity: a randomized community intervention trial. *Am J Public Health* 81:1654-1656

Arroyave G, Aguilar, JR, Flores M et al (1979) *Evaluation of sugar fortification with vitamin A at the national level*. Institute of Nutrition of Central America and Panama-Pan American Health Organization (PAHO). Scientific Publication No. 384.

Arthur P, Kirkwood B, Ross D, et al (1992) Impact of vitamin A supplementation on childhood morbidity in northern Ghana [letter]. *Lancet* 339:361

Bahl R, Kumar R, Bhandari N, et al (1999) Vitamin A administered with measles vaccine to nine-month-old infants does not reduce vaccine immunogenicity. *J Nutr* 129(8):1569-1573.

Barreto ML, Santos LMP, Assis AMO, et al (1994) Effect of vitamin A supplementation on diarrhoea and acute lower-respiratory-tract infections in young children in Brazil. *Lancet* 344:228-231

Beaton GH, Martorell R, Aronson KJ, et al. 1993. *Effectiveness of vitamin A supplementation in the control of young child morbidity and mortality in developing countries*. ACC/SCN State-of-the-art Series Nutrition Policy Discussion Paper No. 13. UNCC/SCN, New York.

Beaton GH and McCabe GP 2000. *Efficacy of intermittent iron supplementation in the control of iron deficiency anemia in developing countries*. The Micronutrient Initiative 2000.

Bhandari N, Bahl R, Sazawal S, Bhan MK (1997) Breast-feeding status alters the effect of vitamin A treatment during acute diarrhea in children. *J Nutr* 127:59-63

Bloem MW, Wedel M, van Agtmaal EJ, et al (1990) Vitamin A intervention: short-term effects of a single, oral, massive dose on iron metabolism. *Am J Clin Nutr* 51:76-79

Chaturvedi S and Aggarwal OP (1999) Pattern and distribution of ocular morbidity in primary school children of rural Delhi. *Asia Pac J Public Health* 11(1):30-33

CINI. 1998. The micronutrient situation in West Bengal.

Coutsoudis A, Bobat RA, Coovadia HM, et al (1995) The effects of vitamin A supplementation on the morbidity of children born to HIV-infected women. *Am J Public Health* 85:1076-1081

Covacev L, Salomone G (1966) Research on plasma levels of vitamin A and beta-carotene in gastrectomized tuberculous. *Annali dell Istituto Carlo Forlanini* 26:349-63

Dibley MJ, Sadjimin T, Kjolhede CL, Moulton LH (1996) Vitamin A supplementation fails to reduce incidence of acute respiratory illness and diarrhea in preschool-age Indonesian children. *J Nutr* 126(2):434-442

Department of Women and Child Development. 1998. India Nutrition Profile. Ministry of Human Resource Development, Government of India.

Donnen P, Dramaix M, Brasseur D, et al (1998b) Malnourished children morbidity following vitamin A supplementation or deworming in Democratic Republic of Congo. *Archives of Public Health* 56:109-124

En-Lin W, Fang YJ, Rong-Hua J, et al (1995) Impact of large doses of vitamin A supplementation on child diarrhoea and respiratory diseases. *Sight and Life Newsletter*, April:3-4

Fawzi WW, Chalmers TC, Herrera MG, Mosteller F (1993) Vitamin A supplementation and child mortality. A meta-analysis. *JAMA* 269:898-903

Galan P, Samba C, Luzeau R, Amedee-Manesme O (1990) Vitamin A deficiency in pre-school age Congolese children during malarial attack. Part 2: Impact of parasitic disease on vitamin A status. *Internat J Vit Nutr Res* 60:224-228

Glasziou PP and Mackerras DEM (1993) Vitamin A supplementation in infectious diseases: a meta-analysis. *BMJ* 306:366-370

ICMR, 2000. District Nutrition Project, Summary of baseline survey on micronutrient deficiency disorders and PEM in five districts.

Iloff PJ, Humphrey JH, Mahomva AI, et al (1999) Tolerance of large doses of vitamin A given to mothers and their babies shortly after delivery. *Nutr Res* 19(10):1437-1446

Khandait DW, Vasudeo ND, Zodpey SP, et al (1999) National vitamin A prophylaxis programme: need for change in current age strategy. *Indian J Pediatr* 66(6):825-829

KGMC, UNICEF, Government of UP Report on Vitamin A deficiency in Bhabraich district (under preparation)

Levin HM, Pollitt E, Galloway R, McGuire J (1993) Micronutrient deficiency disorders. In Jamison DT, et al. *Disease Control Priorities in Developing Countries*, Oxford University Press Oxford, pages 421-451.

Lie C, Ying C, En-Lin W, et al (1993) Impact of large-dose vitamin A supplementation on childhood diarrhoea, respiratory disease and growth. *Eur J Clin Nutr* 47:88-96

McLaren DS, Frigg M. (1997) *Sight and Life manual on vitamin A deficiency disorders*. Basel: Task Force Sight and Life. p. 57

- MI/ UNICEF/Tulane University 1998 *Progress in controlling vitamin A deficiency*. The Micronutrient Initiative, Ottawa
- Mora JO, Dary O, Chincilla D, Arroyave G. (2000) *Vitamin A sugar fortification in Central America: experience and lessons learned*. MOST, Arlington VA.
- NNMB, 1996 Nutritional status of rural population - Report
- National Family Health Survey - 2, India.1998-99 (under publication)
- NFI. 1998. Comprehensive situational analysis study on demand and supply of micronutrient supplements (iron and vitamin A), antihelminths and antimalarials and their consumption patterns in Bhopal Division of Madhya Pradesh 1997-98
- Olson JA (1996) Biochemistry of vitamin A and carotenoids. In *Vitamin A Deficiency: Health, Survival, and Vision* by Sommer A, and West KP, Oxford University Press Inc., New York pages 221-250
- Pandey MR, Daulaire NMP, Starbuck ES, et al (1991) Reduction in total under-five mortality in western Nepal through community-based antimicrobial treatment of pneumonia. *Lancet* 338:993-997
- Paul M and Vidya S (1999) Effect of vitamin A supplementation on vitamin A deficient children suffering from tuberculosis. *Antiviral Research* 36(6):294-301
- Pinnock CB, Douglas RM, Badcock NR (1986) Vitamin A status in children who are prone to respiratory tract infections. *Aust Paediatr J* 22:95-99
- Popkin BM, Solon FS, Fernandez T, Latham MC (1980) Benefit-cost analysis in the nutrition area: a project in the Philippines *Social Science and Medicine* 14:207-16.
- Rahman MM, Mahalanabis D, Hossain S, et al (1999) Simultaneous vitamin A administration at routine immunization contact enhances antibody response to diphtheria vaccine in infants younger than six months. *J Nutr* 129(12):2192-2195
- Rahmathullah L, Underwood BA, Thulasiraj RD, Milton RC (1991) Diarrhea, respiratory infections, and growth are not affected by a weekly low-dose vitamin A supplement: a masked, controlled field trial in children in southern India. *Am J Clin Nutr* 54:568-577
- Ramakrishnan U, Latham MC, Abel R, Frongillo EA (1995) Vitamin A supplementation and morbidity among preschool children in South India. *Am J Clin Nutr* 61:1295-1303
- Ross CA. The relationship between immunocompetence and vitamin A status. In Sommer A, West PW (1996) *Vitamin A deficiency: health survival and vision*. New York: Oxford University Press. pp. 251-273.

- Ross DA, Cutts FT (1997) Vindication of policy of vitamin A with measles vaccination [letter]. *Lancet* 350:81-82
- Ross DA, Kirkwood BR, Binka FN, et al (1995) Child morbidity and mortality following vitamin A supplementation in Ghana: time since dosing, number of doses, and time of year. *Am J Public Health* 85:1246-1251
- Ruel MT, Levin CE (2000) Assessing the potential for food-based strategies to reduce vitamin A and iron deficiencies: a review of the recent literature. IFPRI Discussion Paper 92.
- Scrimshaw NS, Taylor CE, Gordon JE. (1968) *Interactions of nutrition and infection*. Geneva: World Health Organization.
- Semba RD, Muhilal, Mohgaddam NE, et al (1999) Integration of vitamin A supplementation with the expanded program in immunization does not affect seroconversion to oral poliovirus vaccine in infants. *J Nutr* 12(12):2203-2205
- Semba RD, Akib A, Beeler J, et al (1997) Effect of vitamin A supplementation on measles vaccination in nine-month-old infants. *Public Health* 111:245-247
- Semba RD, Munasir Z, Beeler J, et al (1995) Reduced seroconversion to measles in infants given vitamin A with measles vaccination. *Lancet* 345:1330-1332
- Shankar AH, Genton B, Semba RD, et al (1999) Effect of vitamin A supplementation on morbidity due to *Plasmodium falciparum* in young children in Papua New Guinea: a randomized trial. *Lancet* 354(9174):203-209
- Sinha DP, Bang FB (1976) The effect of massive doses of vitamin A on the signs of vitamin A deficiency in preschool children. *Am J Clin Nutr* 29:110-115
- Smurova TF, Prokop'ev DI (1969) Vitamin A and carotene levels in the blood of patients with pulmonary tuberculosis and diabetes mellitus. *Problemy Tuberkuleza* 47:50-5
- Sommer A, Tarwotjo I, Hussaini G, Susanto D (1983) Increased mortality in children with mild vitamin A deficiency. *Lancet* ii:585-588
- Sommer A, West PW. (1996) *Vitamin A deficiency: health survival and vision*. New York: Oxford University Press.
- Stabell-Benn C, Aaby P, Bale C, et al (1997) Randomised trial of effect of vitamin A supplementation on antibody response to measles vaccine in Guinea-Bissau, west Africa. *Lancet* 350:101-105
- Stabell-Benn C, Bale C, Pedro da Silva A, et al (1995) No evidence of fontanelle-bulging episodes after vitamin A supplementation of 6- and 9-month-old infants in Guinea Bissau. *Eur J Clin Nutr* 49:73-74

Stansfield SK, Pierre-Louis M, Lerebours G, Augustin A (1993) Vitamin A supplementation and increased prevalence of childhood diarrhoea and acute respiratory infections. *Lancet* 342:578-582

State Government of Orissa/WHO/NIN. 2000. Report on the safety and feasibility of administering high-dose vitamin A supplements with oral polio vaccine as part of the intensified pulse polio immunization campaign in the State of Orissa, India.

Tabone MD, Muanza K, Lyagoubi M, et al (1992) The role of interleukin-6 in vitamin A deficiency during *Plasmodium falciparum* malaria and possible consequences for vitamin A supplementation. *Immunology* 75:553-554

UNICEF/MI/WHO/MOH-Nepal, 1998 - Nepal Micronutrient Status Survey

Vijayaraghavan K, Radhaiah G, Prakasam BS, et al (1990) Effect of massive dose vitamin A on morbidity and mortality in Indian children. *Lancet* 336:1342-1345

Vitamin A and Pneumonia Working Group (1995) Potential interventions for the prevention of childhood pneumonia in developing countries: a meta-analysis of data from field trials to assess the impact of vitamin A supplementation on pneumonia morbidity and mortality. *Bull World Health Organ* 73:609-619

WHO, 1995 MDIS working paper #2 - Global prevalence of vitamin A deficiency

WHO/CHD Immunisation-Linked Vitamin A Supplementation Study Group (1998) Randomized trial to assess benefits and safety of vitamin A supplementation linked to immunisation in early infancy. *Lancet* 352:1257-1261

WHO/UNICEF/IVACG Task Force. *Vitamin A Supplements: a guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia*, 2nd edition. WHO, Geneva, 1997.