

# Proceedings of the XX International Vitamin A Consultative Group Meeting

## Recommendations for Vitamin A Supplementation<sup>1</sup>

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**ABSTRACT** In all populations where vitamin A deficiency is an important public health problem, prophylactic vitamin A supplements should be given to all infants and young children (0–59 mo), pregnant women and postpartum women within 6 wk after delivery. The efficacy of vitamin A supplementation of young children is one of the best-proven, safest and most cost-effective interventions in international public health. The International Vitamin A Consultative Group (IVACG) also recommends that three 50,000-international unit (IU) doses of vitamin A should be given at the same time as infant vaccines during the first 6 mo of life. Recent kinetic studies have indicated that this regimen will be safe and is necessary to maintain the infant's vitamin A stores, even when the mother is also given 400,000 IU within the first 6 wk after delivery. IVACG will make a decision on whether to recommend prophylactic supplementation of all women of childbearing age when the results of two large trials in Ghana and Bangladesh are available. Active corneal xerophthalmia is always a medical emergency that should be treated with immediate high-dose vitamin A. High-dose vitamin A treatment is also recommended for infants and young children with xerophthalmia, severe malnutrition or measles. Low-dose vitamin A treatment is recommended for women with night blindness and/or Bitot's spots. Given the evidence of the cost-effectiveness of vitamin A supplementation, it is essential that effective vitamin A supplementation programs are made universally available to all populations where vitamin A deficiency is an important public health problem. *J. Nutr.* 131: 2902S–2906S, 2002.

**KEY WORDS:** • *vitamin A* • *nutritional supplementation* • *humans*

Vitamin A supplementation has been extensively researched (1), both in terms of its health and nutritional impact and in terms of the factors that can make supplementation programs successful. Vitamin A supplementation has also been widely implemented, because it is relatively simple and cheap to implement and it is highly cost-effective (2). These recommendations focus exclusively on vitamin A supplementation in populations in which vitamin A deficiency is an important public health problem (3).

Vitamin A supplements are given in two main contexts: as prophylaxis to groups of eligible individuals and as part of the

treatment of sick individuals. These two situations are discussed in turn.

### PROPHYLACTIC SUPPLEMENTATION

Prophylactic vitamin A supplementation of three groups [infants and young children (0–59 mo), pregnant women and postpartum women within 6 wk after delivery] is recommended in all populations in which vitamin A deficiency is an important public health problem.

#### *Older infants and young children (6–59 mo)*

The most severe clinical consequences of vitamin A deficiency (corneal xerophthalmia, severe illness and death) are found mainly in this age group (1), and prophylactic supplementation of older infants and young children (6–59 mo) should be an immediate priority in all vitamin A-deficient populations. The most feasible strategy is to give high-dose supplements every 4–6 mo on a sliding dosage scale on the basis of age (Table 1).

The efficacy of programs that have given a high-dose supplement to at least 80% of all children within this age range every 4–6 mo is one of the best-proven interventions in international public health. A meta-analysis of eight randomized controlled trials (4) showed that, on average, child mortality was reduced by at least 23% [95% confidence interval

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**TABLE 1***Prophylactic vitamin A supplementation recommendations*

Age group	Dose (IU)	Frequency
Infants and young children		
0–5 mo	50,000	With each of the three infant doses of DPT/Polio
6–11 mo	100,000	Every 4–6 months
12–59 mo	200,000	Every 4–6 months
Women 15–44 years		
Within 6 wk after delivery	200,000	Two doses $\geq$ 24 hours apart, for a total of 400,000 IU

(CI)<sup>3</sup> = 12, 32%] (Fig. 1). Further analyses have shown that the percentage of reduction was even greater in those who actually received the doses of vitamin A (5). In populations in which vitamin A deficiency is a problem of public health importance, prophylactic supplementation of this age group is one of the most cost-effective interventions available to public health officials (2).

The recommended dosing regimen has also been shown to be extremely safe. Although such doses cause an absolute increase in reported headache, nausea or vomiting and diarrhea of 3–7%, these short-term side effects are transient, with the large majority (over two thirds) starting and disappearing within 24 h of dosing (6,7). Many millions of older infants and young children have been dosed on this regimen over the past 20 y and more, and no severe side effects have been reported.

More recently, metabolic studies have suggested that the dosing regimen recommended will not cause any important risk of longer-term toxic side effects (8). Furthermore, periodic high-dose supplementation programs to this age group can be quickly implemented on a large scale and rapidly reduce vitamin A deficiency, as evidenced both by improvements in serum retinol concentration (9,10) and by the reduced prevalence and incidence of active xerophthalmia (11–13).

**Young infants (0–5 mo)**

The International Vitamin A Consultative Group (IVACG) endorses the recommendation from a meeting organized by the World Health Organization (WHO) in February 2000 that a dose of 50,000 international units (IU) of vitamin A should be given with each of the three doses of diphtheria, pertussis and tetanus (DPT) that are recommended at (or as soon as possible after) 6, 10 and 14 wk of age (Table 1). This represents a doubling of the dose relative to previous recommendations (14). The rationale for this increase has three main pillars.

First, a large multicenter trial conducted in Ghana, India and Peru showed that, although 25,000 IU of vitamin A given with each dose of DPT at ~6, 10 and 14 wk was very safe, with only a small increase in transient side effects and no increase in other morbidity, this dosing regimen had only a marginal effect on vitamin A status at 6 mo that was not sustained to 9 mo, and it had no significant effect on morbidity (15).

Second, small randomized placebo-controlled trials in Bangladesh of either 25,000 IU (16) or 50,000 IU (17,18) given with each dose of DPT at ~6, 11 and 16 wk revealed similar absolute increases of 8–12% in the incidence of bulging fon-

tanel for both dosages. A much smaller absolute increase in the incidence of bulging fontanel (0.5%) was reported from a much larger trial in Nepal that used a single 100,000-IU dose in 1- to 5-mo-olds (19) and in the multicenter trial (15).

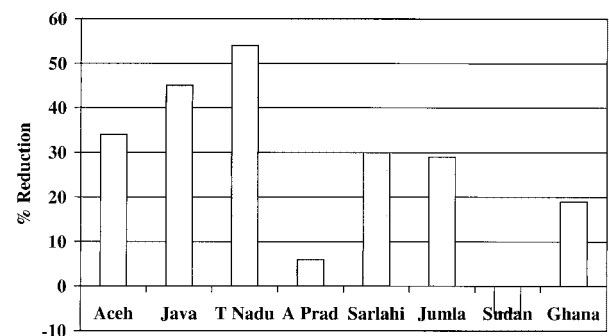
Third, calculations of requirements indicate that even three 50,000-IU doses barely meet requirements in young breast-fed infants of deficient mothers, even if the mother receives a high-dose supplement as soon as possible after delivery (20). Kinetic models of peak liver concentrations and the potential for long-term toxicity showed this dosing regimen should be safe (8).

Although the recommendation to give 50,000 IU of vitamin A with each dose of DPT at or as soon as possible after 6, 10 and 14 wk of age should be implemented immediately, randomized controlled trials (perhaps comparing this regimen with the lower 25,000-IU three-time regimen) are recommended to study the impact of this regimen on vitamin A status and morbidity and mortality, with suitable monitoring of short-term side effects.

Programs should also carefully consider the possibility of introducing an additional 50,000-IU dose of vitamin A given directly to newborn infants as soon as possible after birth. Two randomized, placebo-controlled trials in Asia have now shown this dosage to substantially reduce infant mortality (21,22). The first trial was carried out in infants born in a large hospital in Bandung, Indonesia, and reported a staggering 74% (95% CI = 15, 85%) lower infant mortality in the supplemented neonates (21). Preliminary results from a second trial in Madurai were reported at the recent IVACG meeting in Hanoi (22). These results were also very impressive, with the supplemented neonates having a 21% (95% CI = 1, 37%) lower mortality rate during the first 6 mo of life.

**Pregnant women**

Recent studies in Asia have shown that pregnant and breast-feeding women in poor populations can have a very high prevalence of night blindness and biochemical vitamin A deficiency (23–25). This is likely to be harmful both to the woman and to her infant (26) and argues for considering providing prophylactic vitamin A supplements to pregnant and breast-feeding women or even to all women of childbearing age (13–49 y). High doses of vitamin A should not be given to women within this age range who could be pregnant because of the risk of teratogenic effects in the fetus (6,27). There is strong evidence, however, that a vitamin A dose of up to 10,000 IU given daily, or a dose of up to 25,000 IU given weekly, is safe (8,27). One randomized placebo-controlled trial in Nepal of ~23,000 IU of vitamin A given every week to all

**FIGURE 1** The impact of vitamin A supplementation on mortality in older infants and young children (6–71 mo).

<sup>3</sup> Abbreviations used: CI, confidence interval; DPT, diphtheria, pertussis and tetanus; HIV, human immunodeficiency virus; IU, international unit; IVACG, International Vitamin A Consultative Group; WHO, World Health Organization.

married women of childbearing age has reported a very substantial 40% (95% CI = 3, 63%) reduction in maternal mortality related to pregnancy (28). Further efficacy trials of this intervention are in progress in Bangladesh and Ghana, and IVACG should be in a position to issue a specific recommendation on whether pregnant women (or all women of childbearing age) living in areas where vitamin A deficiency is a public health problem should receive prophylactic vitamin A supplementation as soon as these two trials report their results (expected by 2003).

### Postpartum women

IVACG endorses the recommendation from a meeting organized by WHO in February 2000 (29), that two 200,000-IU doses of vitamin A be given to women within 6 wk after delivery. The two doses should be given at least 24 h apart. This will benefit the woman, because pregnancy and lactation are major drains on the mother's vitamin A stores (30). It will also benefit the infant, because postpartum maternal supplementation (with 300,000 IU) has been shown to increase breast milk and infant serum retinol concentrations for at least 8 mo (31).

Kinetic modeling of this recommendation has shown that at least two 200,000-IU doses are required to maintain adequate breast milk retinol concentrations and that this dosage regimen should be safe (8). Also, a randomized, controlled trial in Zimbabwe that compared 400,000 IU vitamin A given to 400 postpartum women against placebo given to 400 postpartum women has shown no significant increase in short-term side effects either in the women or in their infants (J. H. Humphrey, Johns Hopkins University, personal communication, 2000). The requirement to space the two postpartum doses by at least 24 h arises from concerns that 400,000 IU within a single day might result in transient increases in breast milk retinoic acid (a short-lived metabolite of vitamin A) to toxic levels (B. Underwood, Institute of Medicine, personal communication, 2001). Programmatically, in areas where most mothers either deliver outside official health facilities or leave them within 24 h of birth, this could be achieved either by giving the second dose to the mother to take at home or by using any later contact with the mother within the first 6 wk after delivery to administer the second dose.

### Refugees and internally displaced populations

Several refugee and internally displaced populations have been found to have a prevalence of xerophthalmia in excess of 15% among 2- to 5-y-olds (32). Therefore, refugees and internally displaced populations from developing countries should be treated as having an important public health problem of vitamin A deficiency unless proved otherwise, and they should receive supplementation as a very urgent priority with the same dosing regimen that is used for other populations. The developing country populations who host refugee and internally displaced populations should also receive special attention.

### Delivery channels

The following main delivery channels for vitamin A supplements have been used in large-scale programs: 1) linked to routine immunization or national immunization days alongside polio and/or measles vaccination; 2) as part of other large-scale campaigns, such as national health days (e.g., alongside deworming, provision of other micronutrients) or

national micronutrient days; and 3) as part of the treatment of sick children, such as within the WHO-supported Integrated Management of Childhood Illness Program.

Unfortunately, few routine immunization programs have achieved >50% coverage with at least one dose of vitamin A by the child's second birthday. This is at least partly because health workers often miss this opportunity. For example, a study in northern Ghana by Arhin et al. (33) showed that 55% of infants had an initial contact when they could have received a vitamin A capsule between 6 and 11 mo of age, whereas 48% had a second contact when they could have received a capsule by their second birthday. Conversely, supplementation linked to polio/measles national immunization days has been very successful, with many countries getting one capsule to >80% of young children per year through this route. There is an urgent need to convince governments and donors to sustain similar days twice per year when polio national immunization days are phased out. Incorporating prophylactic vitamin A supplementation into the treatment of sick children is also recommended.

Other program strategies have great potential in certain settings, including the regular provision of vitamin A supplements by health volunteers, as within the Nepal national vitamin A control program (34). Other delivery channels that might have the potential to be exploited include blindness prevention programs, delivery through women's groups or child crèches (day care centers), or inclusion within birthing kits.

Depending on a single delivery channel has the advantage of simplicity and focus, but this advantage needs to be balanced against missing the opportunities afforded by the other potential channels. All vitamin A control programs should systematically review the national and local training manuals and the basic textbooks that are used to train health workers to ensure that vitamin A supplementation (both prophylaxis and treatment) is included in all appropriate places. It should also be included in appropriate amounts within essential drug kits and on essential drug lists.

## TREATMENT

High-dose vitamin A supplements should be included as part of the routine treatment of all individuals with xerophthalmia and of infants and children with severe malnutrition or measles by using the treatment regimens shown in Table 2.

TABLE 2

Vitamin A treatment regimens

	Vitamin A dosage (IU)
Infants and children <sup>1</sup>	
Young infants (0–5 mo)	50,000
Older infants (6–11 mo)	100,000
Children (males: 12 mo or more; females 12 mo to 12 y and ≥50 y)	200,000
Women (13–49 y)	
Xerophthalmia: night blindness and/ or Bitot's spot	10,000 every day or 25,000 every week for at least 3 mo
Active corneal lesions (rare)	200,000 on days 1, 2 and 14

<sup>1</sup> Schedule: severe malnutrition, day 1; measles, days 1 and 2; xerophthalmia, days 1, 2, and 14. Severe malnutrition: kwashiorkor or weight-for-height below -3 sds (NCHS).

### Xerophthalmia

Vitamin A deficiency is the direct cause of xerophthalmia (1). All individuals with xerophthalmia should therefore be treated with vitamin A (Table 2). Improvement of corneal lesions is usually rapid and dramatic. A clinical case series in Indonesia showed that 95% of corneal lesions improved or healed within 1 wk (35). Improvement of active Bitot's spots usually occurs within 2 wk, while the retina is usually the slowest to respond to treatment, with night blindness and poor dark adaptation often persisting for at least 4 wk (35,36). Individuals with xerophthalmia are also at very high risk of death from infectious causes (37), so treating them with vitamin A will substantially reduce this risk. A careful check for infectious diseases such as diarrhea, acute lower respiratory tract infections, measles, tuberculosis and urinary tract infections should always be done in patients with active xerophthalmia.

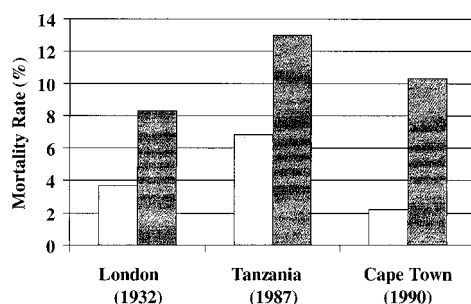
Active corneal xerophthalmia (xerosis or ulcers) is extremely rare in older children and adults, except in severe famines. However, they are a medical emergency, and most individuals with this severe condition go blind within 24–48 h unless they receive effective treatment with vitamin A (35). There is general agreement that the low-dose regimens recommended for the milder forms of xerophthalmia in women of childbearing age do not act quickly enough to save the sight of women with corneal xerophthalmia. Most clinicians and women have accepted that the need to save the sight of the woman outweighs the potential risk to her fetus, even if she is aware that she is pregnant.

### Severe malnutrition and measles

Children with these conditions are also at very high risk of vitamin A deficiency (1), so high-dose supplements should be part of their treatment. Unequivocal data to support this recommendation for measles come from a series of clinical trials in Africa in the 1980s and 1990s (38–41) and a trial conducted in London in the 1930s (42). These trials showed high-dose supplements to have a substantial impact both on mortality (38,39,42) (Fig. 2) and on severe morbidity both during and after the acute measles episode (40,41).

### Other illnesses

In vitamin A-deficient populations, prophylactic high-dose supplements should be given every 4–6 mo to all infants and young children aged 6–59 mo. All children who attend a clinic should be screened to determine whether they have received a dose within the past 4 mo. If not, this opportunity should be used to give them a dose.



**FIGURE 2** Measles treatment and mortality. Light shaded bars, vitamin A supplements; dark shaded bars, comparison.

### HIV infection

The evidence available to date indicates that human immunodeficiency virus (HIV)-positive individuals respond to vitamin A in a similar way to their HIV-negative peers (43,44). Individual HIV infection and a high prevalence of HIV in the population do not affect these recommendations either for prophylactic supplementation or for treatment—they just make them more urgent.

### CONCLUSION

In all vitamin A-deficient populations, initiating and sustaining effective supplementation programs for the at-risk age groups should be an urgent priority. Effective supplementation programs will be those that reach virtually all individuals who are most at risk of vitamin A deficiency. Vitamin A deficiency is a problem that disproportionately affects the poorest individuals within any population (45–47), and poor people are usually those who are the least likely to access public health interventions, so supplementation programs must achieve very high coverage of the total population and must specifically target the poorest and most marginalized groups. Eighty percent coverage of the total target population must be considered an absolute minimum target for vitamin A supplementation programs. Programs that have achieved this minimum must strive for even higher coverage, because the benefits in terms of mortality and morbidity reduction that will be achieved by reaching that last one fifth of the population will be disproportionately large.

Vitamin A deficiency disorders, with their attendant burden of death, sickness and blindness, are a disgraceful example of our world's inability to tackle the extreme inequities that exist within our global, national and local societies. Although humanity has come an enormous way in implementing effective, large-scale vitamin A supplementation programs over the past two decades, and the number of such programs has increased exponentially over the past decade, it is regrettable that such programs still are not available to most of the poorest people in the world.

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