2. EFFICACY OF ORAL VITAMIN A

Considerable research has been directed toward establishing the efficacy of orally administered vitamin A preparations in terms of efficiency of absorption and impact on common indicators of vitamin A status (e.g., serum retinol, clinical xerophthalmia). Efficacy,(52) within the context of preventing vitamin A deficiency and xerophthalmia, incorporates three distinct components: (1) the efficiency of intestinal absorption of oral vitamin A, (2) the retention of oral vitamin A, (3) and the duration for which acceptable vitamin A status can be maintained as a result of the vitamin A dose (i.e., the “protective period”).

EFFICIENCY OF ABSORPTION

Evaluating the absorptive efficiency of vitamin A at different dosage levels and under varying conditions of health and disease is a preliminary step in quantifying the expected improvement in vitamin A status attributable to an oral dose of vitamin A. Efficiency of absorption, in man, may be determined either by computing the difference between the total dose administered and fecal losses of vitamin A for several days after administration, or by quantifying the changes in serum vitamin A levels at specified intervals during the 24 hours following dose administration (“vitamin A absorption curve”), noting the timing and magnitude of the peak rise in serum retinol. In animals, changes in hepatic stores of retinol can also be used to determine the efficiency of absorption.

Figure 3 - Capsules containing doses of vitamin A are given six-monthly by mouth

Figure 4 - In India vitamin A doses are prepared in syrup and given by spoon

TYPES OF PREPARATIONS

Studies over the past fifty years provide evidence about the absorption of vitamin A when administered as an ester or alcohol, in an oil or water-miscible ("aqueous") solution, to healthy or diseased individuals. Human studies have shown vitamin A as an ester (acetate or palmitate) or alcohol to be equally veil absorbed from a healthy gut,(53-55) while in some malabsorptive disorders, the chemical form can influence absorption. For example, in celiac disease both the ester and alcohol are poorly absorbed in oil and well absorbed in aqueous form; in cystic fibrosis, and other malabsorptive diseases, the oil-based vitamin A alcohol may offer an absorptive advantage over the ester in oil.(53)

Vitamin A-replete individuals consistently reveal a markedly higher peak in the 3- to 6-hour serum retinol level following oral administration of aqueous or emulsified preparations versus oil-soluble solutions of vitamin A,(56-60) although comparable serum levels can be noted at 24 hours.(57, 58) Animal experiments have indicated more efficient absorption of megadoses of vitamin A in aqueous and emulsified preparations than in oil solutions,(56, 58) by demonstrating lower fecal loss (5-12% versus 20-23% of the dose), higher peaks in serum retinol, and greater hepatic storage (38-55% versus 23-28%). This can be attributed, in part, to a smaller fat particle size being presented to the intestinal mucosa,(56, 61) and to possible emulsifier-specific influences on vitamin A absorption.(62) Similar differences in fecal excretion levels of vitamin A from both forms have also been reported for healthy infants(58) and adults(63) receiving single doses ranging from 33,000 to 400,000 IU. While these studies suggest there is greater absorption of aqueous vitamin A, satisfactory absorption has been observed after administration of pharmacologic doses of oil-soluble vitamin A to healthy individuals(63-65) and ill patients with normal gut function.(66) Experiments in vitamin A-depleted animals have also demonstrated that aqueous and oil-soluble preparations produce comparable liver stores at 24-48 hours,(67, 68) similar serum values at 24 hours(68) and, most importantly, resolution of xerophthalmic signs accompanied by equivalent rates of growth.(67)

In the presence of severe malabsorptive disease, aqueous vitamin A has consistently been shown to be better absorbed than an oil solution.(63, 65) This is attributed, in part, to less dependence on enzymatic and micelle-forming activities. In the presence of common gastrointestinal infections from giardia,(69) ascaris,(69-71) salmonella,(72) and other entero-pathogenic organisms,(73) vitamin A absorption from both oil-soluble and aqueous preparations is significantly impaired. Following treatment, there is usually marked improvement in absorption.(69, 70, 72, 73)

Severe protein-energy malnutrition, specifically kwashiorkor, causes profound histopathologic changes in the intestinal mucosa(74) and markedly reduces the secretion of pancreatic enzymes into the gut.(75) These changes are likely to account for much of the fat malabsorption accompanying severe PEM.(76) Since children with severe PEM are at greatly increased risk of developing blinding corneal xerophthalmia,(3, 77) improvement in their vitamin A status needs to be accomplished as quickly as possible. Under these conditions, an aqueous vitamin A preparation may be expected to be more rapidly absorbed than an oil solution. Several investigators have observed flat or erratic vitamin A absorption curves following an initial oral dose of up to 75,000 mcg vitamin A in oil among children with frank kwashiorkor and severe xerophthalmia.(74, 78) These observations prompted the original WHO recommendation that such high-risk children, indeed all children with corneal xerophthalmia, be treated initially with intra-muscular aqueous vitamin A.(17, 79) Widely practiced,(7, 78) this treatment appears to be effective in halting and healing corneal destruction, and preventing a relapse for up to one year among surviving children.(7)

Recently however, severely xerophthalmic Indonesian children with moderate to severe PEM or diarrhoea exhibited comparable clinical responses to 200,000 IU oral vitamin A in oil and 100,000 IU vitamin A as an intra-muscular

aqueous injection. Release from the liver into the blood of the vitamin A transport protein (retinol binding protein) 24 hours after treatment suggested adequate absorption of the oil-based vitamin A even when treating such “worst case” clinical profiles.(80) Following these observations the WHO recommendations were revised to include oral administration of 200,000 IU of vitamin A in oil for initial treatment.(17) It was also noted that regardless of the vitamin A preparation and method of administration, children with severe PEM were “at-risk” of early relapse.(3) It is therefore important that these children continue to receive repeated doses of vitamin A periodically while their PEM status improves.(77)

TOXICITY AND CHOICE OF VITAMIN A PREPARATION

Given the evidence, aqueous vitamin A appears to out-perform the oil solution in terms of rapidity of absorption and total vitamin A stored in the liver under conditions of similar gut integrity and general nutritional status. A water-miscible dispersion would appear to be the preferred vehicle for a vitamin A deficiency prevention strategy based on these factors alone. However, for two major reasons aqueous dispersions have not been used for prophylaxis: (1) concern for safety, and (2) the technological problems of packaging a single-unit water-miscible preparation.(62)

Rapid absorption of aqueous vitamin A may result in acute hypervitaminosis A in a significant proportion of children following a large oral dose. The slower absorption rate of oil-based vitamin A is likely to result in an attenuated “spike” in serum retinol and a decreased risk of acute toxicity. Following a single, large oral dose (200,000-300,000 IU), toxicity, commonly evidenced by nausea, vomiting or headache, is self-limited.(42) The literature related to hypervitaminosis A toxicity in children attributable to oral dosing with large amounts of vitamin A has been extensively reviewed by the International Vitamin A Consultative Group (IVACG).(51) In one study,(81) nearly 25% of the children developed toxic manifestations following oral administration of a single dose containing 300,000 IU of a water-miscible preparation, while three other studies reported no toxic symptoms. Ten investigations using vitamin A in oil, ranging from 165,000 to 330,000 IU with or without added vitamin E, reported no toxic symptoms, while seven others reported transient signs of toxicity in up to 4% of recipient children.(51) In Indonesia, a somewhat higher incidence of vomiting and diarrhoea (16%) has been recently reported following administration of 300,000 IU in oil,(31) although a markedly lower toxicity rate of 6% was noted when 250 IU of vitamin E were added. During recent, carefully supervised studies of some 50,000 children in India receiving 200,000 IU vitamin A in oil every 6 months, vomiting or diarrhoea was noted in only 0.7% of the children.(82) Thus, reduced risk of toxicity appears to attend the use of an oil solution, although even a low incidence of mild symptoms could severely reduce future compliance in a population-based programme.

The second problem deals with the practicalities of designing an efficient production and delivery system at low cost which maintains vitamin A stability and potency over extended periods of time under a range of environmental conditions. An oil solution can be readily encapsulated in a gelatin shell or enclosed in a bottle, remains potent under ambient temperatures during storage periods of over three years,(43) and does not run the same risk of separation over time as does an aqueous dispersion.

These concerns for safety and practicality directed the development of vitamin A delivery systems using a standard 200,000 IU dose in oil, which has become the recommended preparation for nearly all direct-dosing supplementation programmes. The remainder of this paper deals primarily with the efficacy of oral, oil-based preparations, and the

effectiveness and costs of country programmes utilizing oil solution.

RETENTION OF OIL-SOLUBLE VITAMIN A

A number of studies in India have been conducted on both absorption and retention of oil-soluble vitamin A in apparently normal and ill children in physiologic and large pharmacologic doses.(70, 83-86) Table 2 lists these studies by dosage of vitamin A and health status of the subjects. “Healthy” children lacked clinical evidence of infection, though in one study they were reported to be substandard in weight and height.(85) Several important and consistent findings are apparent regarding the absorption and retention of vitamin A in oil:

1. When administered in physiologic amounts (approximately 3,000 IU) to apparently normal children, oil-soluble vitamin A is nearly completely absorbed and is approximately 80% retained.(70, 83, 85)

2. In the presence of systemic and enteric infection, absorption is reduced to 75% and retention to some 60-65%; (70, 83) however, retention of the total amount actually absorbed remains at approximately 80%, suggesting reduced absorption is responsible for lover retention.

3. In healthy preschool children, of a large dose (e.g., 200,000 IU) of oil-soluble vitamin A, only 70% is absorbed,(84-86) and 40-50% of the total dose is retained(86) (or 65% of absorbed dose).

TABLE 2

RECENT STUDIES FROM INDIA REPORTING PERCENT ABSORPTION AND RETENTION OF ORALLY ADMINISTERED, OIL-SOLUBLE VITAMIN A PREPARATIONS AMONG CHILDREN

Authors	(Ref)	No.	Age (years)	Clinical status	DOSAGE		Ester form	% dose absorption	% dose retention
					IU	mcgRE			
I. Physiologic dose, healthy children									
Sivakumar and Reddy	(85)	5	2-4	normal*	3,000	900	palmitate	96±21	80±1
Sivakumar and Reddy	(83)	5	2-10	normal	2,900	873	acetate	99±1	82±2
Sivakumar and Reddy	(70)	5	2-6	normal	3,300	1,000	NR2	99±1	82±2
II. Physiologic dose, ill children									
Sivakumar and Reddy	(83)	5	2-10	resp. infection	2,900	873	acetate	74±7	58+6
	(83)	3	2-10	diarrhea	2,900	873	acetate	70+1	NR
Sivakumar and Reddy	(70)	6	2-6	ascariasis	3,300	1,000	NR	80+3	68+4

III. Pharmacologic dose, healthy children									
Sivakumar and Reddy	(85)	5	2-4	normal*	200,000	60,000	palmitate	67+4	47+4
Pereira and Begum	(84) (4)	6	4-5	normal	182,000	54,000	palmitate	75+4	38+13
Kusin et al	(3)	7	3-6	normal	200,000	60,000	NR	68+3	49+3
	(86)	7	3-6	normal	200,000	60,000	NR	73+3	50+3
	(5)	3	3-6	normal	200,000	60,000	NR	82+2	55+2

1 Mean percent absorbed +1 SD.
2 Not reported.
3 4 children received 40 mg vitamin E.
4 Plus 100 mg vitamin E.
5 Plus 500 mg vitamin E.

* Undernourished by weight and height.

It has been suggested that 30-50% of the 200,000 IU dose of vitamin A is retained;(79) the above studies imply that higher levels of retention may best relate to children who are free from overt infection or advanced malnutrition (Table 2). (Calculations of retention subtract the amount excreted in the first few days after the dose.) In the presence of enteric infection, markedly reduced absorption and therefore retention of a large dose of vitamin A is likely to occur.(53, 69, 71, 72) In addition, common respiratory infections, during which absorption of physiologic doses of vitamin A decreases from nearly 100% to about 75%,(83) may be expected to also reduce absorption of a large dose of vitamin A. During respiratory tract and other infections, metabolic losses of vitamin A are increased, sometimes dramatically (³3000 IU/day),(87-89) which may further reduce retention. Given the hyperendemicity of gastrointestinal and respiratory tract infections among undernourished populations where periodic vitamin A supplementation is needed, as little as 20-30% of the large oral dose may be retained.(70)

THE PROTECTIVE PERIOD

THEORETICAL ESTIMATES

The prophylactic efficacy of a large, oral dose of vitamin A in preventing vitamin A deficiency and xerophthalmia is ultimately determined by the period of protection conferred upon “at-risk” individuals known to have received the

vitamin A supplement.

A variety of models have been employed to compute a theoretical time interval during which acceptable vitamin A status would be achieved and maintained following receipt of a 200,000 IU dose. Assuming 50% retention, WHO has estimated a protective period of about 100 days for a young, growing child.(79) This estimate applies most suitably to a clinically normal child, weighing approximately 15 kg, requiring 20 mcg retinol equivalents (RE) (91)/kg body weight per day,(92) and consuming a diet nearly devoid of vitamin A. Thirty percent retention would decrease this interval to 60 days. Under conditions in which half of a one- to three-year old child's recommended allowance, or about 200 mcg RE,(93) is provided by the diet,(30) these intervals would be extended to 200 and 120 days, respectively.

The above estimates assume a linear rate of retinol depletion from the liver over the stated time period. Models based on animal data indicate that release of vitamin A from the liver is an exponentially decaying function of the adequacy of hepatic stores. That is, in the presence of significant reserves, retinol leaves the liver at a relatively high rate, but in the depleted state the rate of hepatic release is lower.(90, 94) This liver-depletion-rate model has been adapted to estimate the protection period against xerophthalmia in a typical 10-kg child (Figure 5) Again, assuming 50% retention, a 200,000 IU dose of vitamin A would provide approximately 30 mg of stores, conferring protection for about 240 days. The protective period against severe, blinding corneal xerophthalmia should be even longer than that for milder disease.

Under this model, the longer protective period should be interpreted with caution since a decreasing rate of hepatic release of retinol over time would produce a concurrent, gradual decline in vitamin A nutriture throughout all dependent body tissues. Even if the protective period for corneal lesions is extended, prolonged systemic depletion of vitamin A during the pre-xerophthalmic state is likely to carry other risks. Studies among animals only marginally depleted in vitamin A have clearly demonstrated reduced rates of growth and significant atrophy of the thymus and other lymphoid organs.(95) In addition, epithelial tissue integrity,(96, 97) mucus production, and phagocytosis are adversely affected by vitamin A deficiency,(98) compromising resistance to infection.

Evidence is now emerging from human studies which corroborates animal data indicating increased susceptibility to infection in the presence of milder stages of xerophthalmia.(10) Results from the Indonesian Nutritional Blindness Prevention Project indicate that children with night blindness and Bitot's spots may be at three times the risk of developing diarrhoea, and twice the risk of developing respiratory infection as children without “mild” xerophthalmia.(10) Findings from a large randomized community trial to evaluate vitamin A supplementation in northern Sumatra showed a 34% reduction in mortality attributable to the programme, suggesting an increased risk of dying to be present even among non-xerophthalmic children who live in areas of endemic dietary vitamin A deficiency.(99) Thus it may be that the latter stage of a “protective” time interval is more of a “latent period,” during which ordinarily inapparent but significant systemic deficiency is developing.

PROTECTION AGAINST LOW SERUM RETINOL LEVELS (100)

One widely used indicator of vitamin A status is the level of vitamin A in the serum, usually expressed as micrograms of retinol per decilitre (mcg/dl). While serum retinol levels bear reasonable correspondence to vitamin A stores in the

low ranges of status, it is recognized that indicator accuracy becomes more suspect at higher serum levels.

Figure 5 - Estimated Relationship Between Total Body Vitamin A and the Period of Protection Against Vitamin A Deficiency[90, 94]

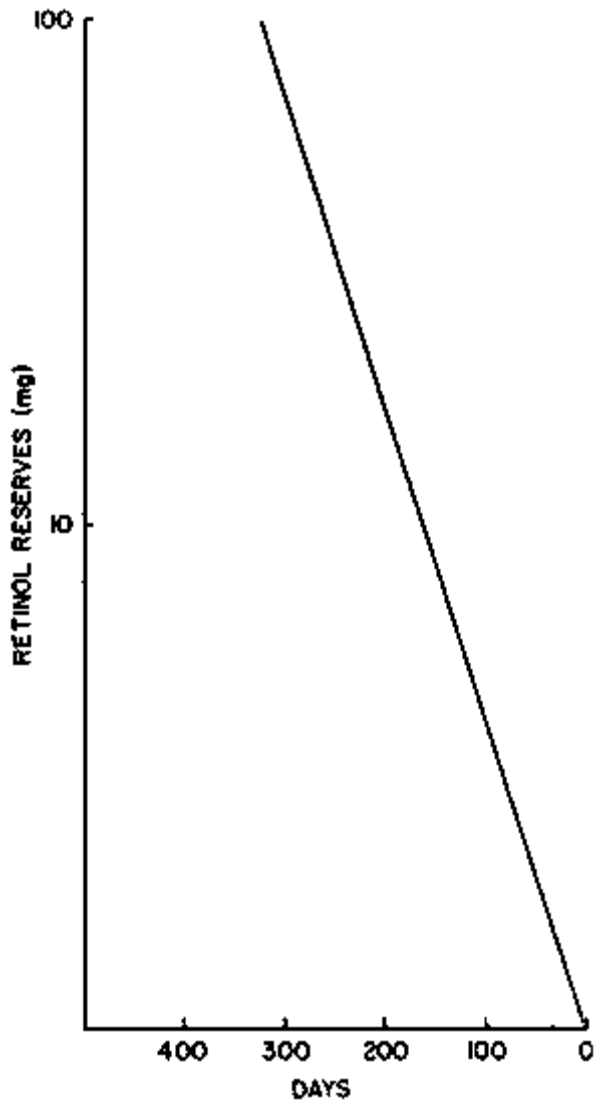

Table 3 summarizes controlled studies that prospectively investigated the effects of a single large oral dose of vitamin A on serum retinol levels. Firstly, while each study has an acceptable comparison group, follow-up varies between studies, from essentially complete at six months(31) to approximately 50% at 22 weeks.(101) Secondly, the vitamin A

dosage employed varies from study to study, ranging from 50,000 to 300,000 IU. Thirdly, subjects were followed for varying periods of time. And lastly, the populations differed markedly in their baseline vitamin A status, and presumably in their subsequent level of dietary vitamin A intake.

Results of a single large oral dose of vitamin A, in Table 3, do not leave a clear impression of long-term efficacy in maintaining elevated serum retinol levels. The study of healthy, breastfed newborns by Thanangkul et al.(102) suggests a prolonged elevation of serum retinol above control levels for up to 7.5 months ($p<0.01$), following a single supplementation with 50,000 IU of retinyl palmitate. Although the control infants also had normal vitamin A levels (>20 mcg/dl) during the first 36 weeks (values not shown in Table 3) without any vitamin A supplement, their serum retinol levels had fallen below 20 mcg/dl at 42 weeks, while supplemented group levels remained normal (18 vs 32 mcg/dl, respectively).

In Jordan, Patwardhan et al.(47) demonstrated similar elevations of serum retinol levels above baseline ($p<0.01$) in both 300,000 IU and placebo recipient infants after two months. After twelve months (not shown in Table 3) only 50% of the infants were successfully followed; serum retinol levels were still similar and acceptable in both groups, (29 versus 26 mcg/dl, respectively), i.e. no effect of a 300,000 IU vitamin A was observable in this study.

In India, Pereira and Begum(103) demonstrated that two weeks following a 182,000 IU oral dose of retinyl palmitate, vitamin A remained some 7 mcg/dl higher in experimental versus control group, among two- to five-year-old children with normal baseline serum retinol values. Both groups had an apparently acceptable baseline vitamin A status despite having received a low beta-carotene diet (300 IU or 30 mcg RE/day) for three months prior to the study. Though this difference was not statistically significant between two weeks and ten weeks, the supplemented recipients appeared to retain more serum retinol for over 10 weeks, after which average serum retinol values steadily decreased to low levels in both groups. Subsequent re-dosing of the same amount to the same children, including the previous control group, elevated serum levels to approximately 30 mcg/dl one week later. The average concentrations remained at or above 20 mcg/dl for 11-15 weeks following this dosage (not shown in Table 3).

In a second study by these same authors among children with low baseline vitamin A status,(104) the ability of a single 50,000 IU dose of retinyl palmitate to elevate and maintain serum retinol levels was influenced by the quantity of beta-carotene in the diet. The supplement had no effect when recipient and control children regularly consumed some 15-30 grams of dark green leaves per day (approx. 150 mcg RE) throughout the 18 week follow-up period (not shown in Table 3). However, during a beta-carotene deficient diet (approx. 20 mcg RE/day), vitamin A supplemented children displayed significantly and acceptably elevated serum retinol levels for up to eight weeks compared to the low concentrations among unsupplemented controls, as shown in Table 3. After that time, levels among the supplemented children gradually decreased, becoming deficient by 18 weeks (12±3 mcg/dl). Pereira and Begum(105) had already shown that a diet of 30 grams of dark green leafy vegetables per day for three months could elevate serum vitamin A levels from a baseline of 22 mcg/dl to 32 mcg/dl. More importantly, when a group of these same children were later placed on a controlled, low beta-carotene diet (30 mcg RE/day), serum retinol continued to remain at acceptable levels (>20 for mcg/dl) for more than five months.

TABLE 3

CONTROLLED STUDIES ON THE EFFICACY OF A SINGLE LARGE ORAL DOSE OF VITAMIN A TO ELEVATE AND MAINTAIN SERUM RETINOL LEVELS FOR EXTENDED PERIODS OF TIME

Authors (Ref)	Country	Age	Dosage (in 000's)	Number		Follow up period	Serum retinol (mcg/dl)±SD	
				E(1)	C(2)		E(1)	C(2)
Patwardhan et al.(47)	Jordan	0-6 mos	300 IU	57	58	Initial	14+10	17+7
				57	58	8 wk	26+20	26+23
Pereira and Begum (103)	India	2-5 yrs (healthy)	182 IU	14	16	Initial	26+8	25+7
				14	16	2 wk	28+7(a)	21+6
				14	16	10 wk	25+9	22+5
				14	16	25 wk	14+6	12+3
Pereira and Begum (104)	India	2-6 yrs (healthy)	91 IU	12	12	Initial	13+4	13+3
				12	12	2 wk	29+6(c)	15+3(d)
				12	12	8 wk	20+6(a)	15+4(b)
				12	12	18 wk	12+3	11+2
Thanangkul et al. (102)	India	newborns (healthy)	50 IU	62	59	Initial	15+1	13+1
				62	59	18 wk	29+2(c)	20+1(d)
				62	59	30 wk	37+3(a)	26+2(b)
				62	59	42 wk	32+5(a)	18+3(d)
Dhanamitta et al. (101)	Thailand	preschool	100 IU (24 mos) or 200 IU (£24 mos)	78	78	Initial	14	15
				54	54	10 wk	22	18
				39	39	22 wk	19	17
Kusin et al. (31)	Indonesia	1-5 yrs	300 IU	134	134	Initial	16+6	16+6
				99	85	12 wk	18+8	18+6
				134	134	24 wk	16+6	17+8

(1) Experimental group
(2) Comparison group (control or placebo)
a, b: difference significant at (0.01 < p <0.05) level
c, d: difference significant at (p < 0.001) level.

In Indonesia, Kusin and colleagues(31) found that a 300,000 IU supplement had no demonstrable effect on serum retinol measured after 3 and 6 months, among one- to five-year-old children with marginal baseline vitamin A status. Dhanamitta et al.(101) similarly demonstrated little or no discernible effect associated with a 100-200,000 IU

supplement throughout 5 1/2 months of observation. In Brazil, Araujo et al.(106) have also reported no difference from baseline serum retinol levels 4 weeks after a 200,000 IU dose was administered to poor children consuming a low vitamin A diet (not shown in Table 3).

The critical importance of an appropriate concurrent comparison group in evaluating these results is obvious from the sometimes dramatic shifts in serum retinol levels, in either direction, observed over time from influences unrelated to the intervention itself.(47, 102, 103) In both the Jordanian and Thai infant studies(47, 102) in particular, lacking control groups, the data would have suggested a strong and persistent impact of the vitamin A supplement on serum retinol levels. However, inclusion of control groups showed the actual dose effect to be minimal or absent.

Based on these studies, the period during which elevated serum retinol levels can be maintained in children who initially exhibit low or marginal vitamin A status is highly variable, with optimistic estimates ranging from 8 to 42 weeks. Dietary intake of as little as 150 mcg RE/day from dark green leafy vegetables or other dietary sources of provitamin A may lengthen this period of protection.

PROTECTION AGAINST XEROPHTHALMIA(107)

The efficacy of large-dose vitamin A distribution in protecting against xerophthalmia was first suggested by results from a two-year field trial conducted in India,(49) during which 1785 one- to five-year-olds received an oral dose of 300,000 IU in oil once a year. The study design included no comparison group and the results suffer from a nearly 50% attrition rate at the two-year follow-up. Given these limitations, an 87% “prophylactic efficacy”(108) against Bitot's spots among three- to five-year-olds can be computed according to guidelines provided by Milton(109) for a pre-/post-intervention study design. While this effect cannot be entirely attributed to the annual dose of vitamin A, given the usual seasonal patterns of xerophthalmia and other influences on vitamin A status, the estimate is quite similar to those derived from better controlled studies noted below.

Table 4 presents results from three controlled clinical studies in which the follow-up period after each single vitamin A dose ranged from four to six months. In a study by Tarwotjo et al.(110), 2,680 one- to five-year-old, urban and rural, Indonesian children were examined and enrolled in a large-dose supplementation trial, with alternate assignment to either a vitamin A capsule or placebo capsule in a double masked fashion. The overall baseline prevalence of xerophthalmia was 4.7%. Children were carefully monitored for correct capsule receipt status, and 92% of the subjects were re-examined for xerophthalmia six months later, at which time a second vitamin A or placebo capsule was administered to children by the examination teams. At twelve months, 85% of the originally enrolled children were again examined for xerophthalmia. The findings show a striking and statistically significant difference in the six-month incidence of conjunctival xerosis and Bitot's spots: 0.5% among the capsule recipients versus 3.6% among placebo children, resulting in a prophylactic efficacy of 86%. Also, xerophthalmic lesions had completely regressed among 91% of the initial cases who were treated with a single 200,000 IU dose and successfully followed up at the six-month interval. Still, nearly 10% of the Bitot's spots persisted, representing either failure in efficacy or sequelae from previous vitamin A deficiency that was no longer active, a sign often found among older children.(111) At twelve months (six months after the second capsule distribution), prophylactic efficacy remained at 90%, reflected by six-month incidence rates of 0.3% and 2.9% ($p < .001$) among vitamin A supplemented and placebo children, respectively.

During the Ichag Study in India,(112) Sinha and Bang reported equally striking differences in the incidences of night blindness (XN) and Bitot's spots (X1B) between preschool children receiving, in a double-masked design, either a 200,000 IU vitamin A or placebo capsule every 4 months. The seasonal dynamics of xerophthalmia incidence, in addition to numerous other disease and nutritional factors operating in the village, were first monitored for two years.(113) The vitamin A capsule and placebo intervention study then began during a third, subsequent year and children were followed each month for 10 months. Night blindness was essentially eliminated after the first vitamin A dosing and throughout the entire period of observation, while the prevalence of X1B was reduced by approximately 50% during the peak incidence season.(112) Receipt of the vitamin A capsule had no effect over the placebo in preventing recurrent Bitot's spots during the peak season among children who had exhibited X1B during the previous year.

TABLE 4

CONTROLLED STUDIES ON THE EFFECT OF A SINGLE LARGE ORAL DOSE OF VITAMIN A TO PREVENT XEROPHTHALMIA FOR AN EXTENDED PERIOD OF TIME

Authors (Ref)	Country	Age	Dosage (000)	Number		Follow up period	Incidence or Prevalence of Xerophthalmia			
							XN		Clinical Signs(3)	
				E(1)	C(2)		E	C	E	C
Tarwotjo et al. (110)	Indonesia	12-60 mos	200 IU every 6 months	1340(4)	1340(4)	Initial	NR(5)	NR	4.7%*	4.7%*
				1286	1183	6 mos	NR	NR	0.5%#(c)	3.6%(d)
				1197	1072	12 mos	NR	NR	0.3%#(c)	2.9%(d)
Sinha and Bang (112)	India	2-5 yrs	200 IU every 4 months	153	153	Initial	3.0%*	3.0%	7.0%*	7.0%
				153	153	4 mos	0.0%*	4.0%	10.0%*(a)	19.0%(b)
				153	153	8 mos	0.0%*	1.0%	5.0%*	7.0%
Kusin et al. (31)	Indonesia	1-5 yrs	300 IU	142	147	Base	NR	NR	2.7%#	2.1%
						6 mos	NR	NR	1.3%#	0.0%

(1) Experimental group
(2) Comparison group (control or placebo)
(3) X1A and/or X1B
(4) Approximate allocation
(5) Not reported
* Prevalence data
# Incidence data

a, b difference significant at (0.01 p 0.05) level
c, d difference significant at (p 0.001) level

Newly incident cases, however, were reduced from 8.8% among controls to 0.8% (not shown in Table 4), among supplemented children ($p < 0.004$), reflecting a degree of efficacy (91%) similar to that observed in Indonesia(110) and elsewhere in India.(49)

In a field trial conducted in North Sumatra, a six-month follow-up study showed no effect of a 300,000 IU dose of oral vitamin A on the occurrence of xerophthalmia.(31) Given the small number of cases observed in this study, these results neither support nor refute vitamin A large-dose efficacy in preventing clinical vitamin A deficiency.

Treatment of a sufficient number of outpatient children exhibiting mild xerophthalmia with a single, oral dose of vitamin A and observing their relapse rate over time may be most analogous to testing the prophylactic efficacy of a community-based strategy which successfully reaches those children most “at-risk” of developing corneal xerophthalmia. Sommer observed 48 Indonesian children with Bitot's spots who were eligible for examination at monthly intervals for up to 14 months following administration of a single 200,000 IU oral dose of vitamin A.(3) A modified life table analysis indicated no relapses at five to six months, with a 5 to 11% relapse rate at seven to fourteen months (Table 5).

TABLE 5

RELAPSE RATE OF BITOT'S SPOTS AMONG PRESCHOOL AGE INDONESIAN CHILDREN TREATED WITH A SINGLE 200,000 IU VITAMIN A CAPSULE

Follow-up(1)	Eligible for exam	Examined		Relapsed		
(months)	No.	No.	%	No.	%	Cum. %
1-2	48	33	68.8	0	-	-
3-4	47	20	42.6	0	-	-
5-6	44	19	43.2	0	-	-
7-10	35	19	54.3	1	(5.3)	5.3
11-14	24	18	75.0	1	(5.6)	10.9

(1) Maximum number of months for which treated children could be followed prior to termination of the study.

Data from Sommer. (3)

If a single, large dose of vitamin A is successful in treating corneal xerophthalmia, then it should also bolster vitamin A stores sufficiently to prevent corneal xerophthalmia (X2/X3) from developing in vitamin A-depleted children who have not yet developed corneal lesions. However, data on treating children with corneal xerophthalmia using a single dose of vitamin A is sparse. In Indonesia, 10 severely protein-energy malnourished children with corneal lesions were treated with a single 200,000 IU oral dose of vitamin A on an outpatient basis.(3) During the subsequent two weeks, 67% of the 15 diseased eyes (9 children) that were successfully followed were cured, while the remaining 33% had

improved. One severely malnourished two-year-old child developed punctate keratopathy by the fifteenth day after treatment. Hospitalization was refused by the mother, and on the twenty-third day a house visit examination revealed bilateral, moderate corneal xerosis with ulcerations. Despite further treatment at that time the child expired two days later. Corneal deterioration also occurred in a second child within three months of receiving the single dose. The remaining 8 children showed no signs of relapse within six months after receiving the single dose, although one severely malnourished child developed corneal xerosis eight months after treatment. These few observations permit a cautious estimate of up to several months protection against corneal disease associated with a single 200,000 IU dose in children who are initially severely vitamin A-deficient and moderately to severely protein-energy malnourished. The early failures that occurred indicate that corneal xerophthalmia can respond to a single oral dose of vitamin A despite severe protein energy malnutrition, but absorption, storage and subsequent utilization may be too markedly impaired to achieve sustained protection.

Recently, Indian investigators have concluded a four-year, hospital-based, case-control study of the efficacy of 200,000 IU of vitamin A given every six months to prevent corneal xerophthalmia.(114) Children with corneal xerophthalmia (n = 32) and their nutritional status-matched controls (n = 99) from 375 slums in Hyderabad and Secunderabad were questioned about their previous receipt of at least one large dose of vitamin A during the previous year in the community. Over 90% of all cases were severely protein-energy malnourished. Ninety-four percent of the cases versus 55% of the controls had not received a large dose of vitamin A from a programme which had achieved an overall coverage of 87%. An odds ratio of 12.5 (95% confidence limit: 3.2, 49.5) was computed to approximate the relative risk of developing corneal xerophthalmia among severely malnourished children who did not receive a vitamin A dose in the intervention programme. The efficacy of the 200,000 IU vitamin A dose in preventing corneal xerophthalmia was 92% [e = 100(12.5-1/12.5)]. Assuming that cases and controls broadly represent their respective populations “at large” of malnourished children in these slums, this study provides the first quantifiable estimate of risk protection against severe xerophthalmia conferred by a 200,000 IU dose of vitamin A. Moreover, incidence of corneal xerophthalmia, measured by monitoring hospitalized cases from study areas, decreased more than four-fold from 0.47 to 0.10 per 1,000 per year in distribution areas during the four-year study, while incidence in non-programme slums varied between 0.80 to 0.60 per 1,000 during this same time period.(114)

Evidence from controlled and other supportive clinical studies suggest a 90% or better protection against developing mild xerophthalmia for at least four to six months. A similar high degree of protection appears to be conferred against corneal disease as well. These conclusions support the use of supplementary vitamin A to prevent vitamin A deficiency and nutritional blindness.