Reprinted from the Archives of Ophthalmology
February 1988, Volume 106

Impact of Vitamin A Supplementation on Xerophthalmia

A Randomized Controlled Community Trial

Edi Djunaedi, MD; Alfred Sommer, MD; Akbar Pandji, MD; Kusdiono, MD; Hugh R. Taylor, MD; the Aceh Study Group

• The value of biannual distribution of 200 000 IU of vitamin A in preventing xerophthalmia was assessed in a randomized, controlled community-based trial involving 25 000 preschool children in 450 villages of northern Sumatra. Results indicate that distribution was associated with a dramatic decline in xerophthalmia prevalence; that concurrent controls were critical for distinguishing spontaneous from program-related changes; and that the apparent level of benefit depended on the choice of clinical indicator(s). Night blindness ceases to be an accurate reflection of impact when prevalence rates are low, and comparison of Bitot's spot rates should be confined to new cases of disease.

(*Arch Ophthalmol* 1988;106:218-222)

Vitamin A deficiency remains a major cause of morbidity and mortality throughout the developing world.[1-4] An estimated 5 million children develop xerophthalmia in Asia yearly—with a quarter million becoming blind.[5,6] Estimates for Africa are less reliable although xerophthalmia alone, or in association with measles, is clearly a major cause of childhood blindness.[7-9]

Periodic administration of massive doses of vitamin A, typically 200 000 IU every six months, remains the most popular, widely implemented means of controlling xerophthalmia.[10,11] Data indicating the effectiveness of this approach are limited to uncontrolled observations,[12] follow-up of treated patients,[6] a small-scale study of thrice-yearly distribution in a single village,[13] an unpublished report of biannual distribution in four villages,[14] and an imaginative attempt to use retrospective analyses to assess a nationwide program.[15,16] The latter study, which inferred that Bangladesh's nationwide program had limited value because the prevalence of Bitot's spots was unrelated to mass-dose vitamin A coverage and xerophthalmia rates were still greater than World Health Organization standards, was hampered by the problems of recall, selection bias, the ecologic fallacy of assuming areas with high and low coverage had similar, inherent baseline risks of xerophthalmia, and the inability to distinguish between new and old (persistent and recurrent) cases of Bitot's spots. A small-scale comparative study of alternative intervention strategies in the Philippines concluded that mass dosing was largely ineffective.[17]

We report herein the first (to our knowledge) large-scale randomized controlled community trial of the efficacy of biannual mass-dose vitamin A prophylaxis in reducing the risk of subsequent xerophthalmia. Results indicate significant benefit, a direct relationship between participation and response, and the importance of prospective, concurrently controlled evaluation and careful choice of clinical indicators.

Accepted for publication Oct 2, 1987.

From the Ministry of Health, Government of Indonesia, Jakarta (Drs Djunaedi, Pandji, and Kusdiono); the International Center for Epidemiologic and Preventive Ophthalmology, Dana Center of the Wilmer Institute and School of Hygiene and Public Health, The Johns Hopkins University, Baltimore (Drs Sommer and Taylor); and Helen Keller International, New York (Dr Sommer).

Reprint requests to the International Center for Epidemiologic and Preventive Ophthalmology, Wilmer 120, The Johns Hopkins Hospital, 600 N Wolfe St, Baltimore, MD 21205 (Dr Sommer).

SUBJECTS AND METHODS

The background and methods have been detailed previously.[3] Continued editing and "cleaning" have resulted in a modest increase in the proportion of subjects with complete records. In summary the study was carried out in 450 villages of northern Sumatra that were randomized to either begin a mass-dose distribution program shortly following baseline examination (program villages, n = 229) or one year later (control villages, n = 221). Health center personnel throughout the study area were instructed in the diagnosis and treatment of xerophthalmia, so the government could compare the effects of "universal" provision to all village children (UNIVAC) with those of "targeted" delivery to children presenting with active disease (TARVAC).

Two study teams, each consisting of an ophthalmologist (team leader), a nurse, an anthropometrist, a dietitian, five enumerators, and a driver, all fluent in the local dialect (Acehenese), visited each village in random order with no knowledge of their program allocation. Enumerators visited every house containing children 0 to 5 years of age; collected socioeconomic, demographic, and medical data; and escorted the children to a central point for their clinical examination. Dates of birth were ascertained by a "local events" calendar.

The ophthalmologist, who examined the children's eyes with a focused light and ×2 loupes, classified abnormalities according to standard diagnostic criteria.[18] Parents were carefully questioned about the pres-

ence of night blindness. A carefully elicited history of night blindness, the presence of Bitot's spots, and the two conditions together are closely correlated with serum vitamin A levels.[19]

All children with xerophthalmia were treated with a large dose of vitamin A and referred to the local health center. Baseline examinations were conducted between September 1982 and August 1983. Follow-up visits were made by the same team in the same sequence nine to 13 months later.

Following baseline examination, the government nutrition service trained a local village volunteer to administer standard capsules supplied by the United Nations Children's Fund (200 000 IU of vitamin A and 40 IU of vitamin E) to every child 1 to 5 years of age by snipping off the capsule's nipple and expressing the contents directly into the child's mouth. Initial distribution took place one to three months following baseline examination; the second distribution took place six to eight months later. The local volunteers were neither trained nor encouraged to carry out other health promotion activities. A special distribution monitor visited each village two to four weeks after the scheduled distribution and interviewed 10% of eligible households. If coverage was less than 80%, the local distributor was encouraged to reach children previously missed.

All data were collected on precoded forms, entered onto diskettes, and shipped to the data management facility at the International Center for Epidemiologic and Preventive Ophthalmology, Baltimore, where the information was processed with the Scientific Information Retrieval (SIR) data management package run on a computer (IBM 4341). Statistical analyses utilized SIR, SAS, SPSS, and GLIM software. Tests for significance and construction of confidence intervals were adjusted for clustering (design effect) associated with randomization by village rather than by individual.[3]

All study procedures were approved by a steering committee consisting of representatives from the Indonesian Center for Nutrition Research, the Directorate of Community Health Services, provincial health authorities, The Johns Hopkins University, Baltimore, and Helen Keller International, New York. All children, regardless of village allocation, received a vitamin A capsule at the concluding examination.

At the baseline examination, 29 493 preschool-age children were enumerated. Follow-up information was available on 26 268, representing 89.3% of those from program (UNIVAC) villages and 88.9% from control (TARVAC) villages. The age and sex distribution of children lacking follow-up information was identical in the two groups.

RESULTS

Details of the initial ocular examination are available on 96% of the cohort of UNIVAC and 95% of

Table 1.—Age-Specific Xerophthalmia Rates at Baseline Examination*

Age, mo	Program (UNIVAC) Villages			Control (TARVAC) Villages		
	No. of Children	XN, No. (%)	X1B, No. (%)	No. of Children	XN, No. (%)	X1B, No. (%)
0-11	1992	0 (0.00)	1 (0.05)	1875	0 (0.00)	3 (0.16)
12-23	1946	5 (0.26)	7 (0.36)	1895	6 (0.32)	10 (0.53)
24-35	2107	31 (1.47)	27 (1.28)	2041	25 (1.22)	21 (1.03)
36-47	2268	31 (1.37)	35 (1.54)	2026	47 (2.32)	44 (2.17)
48-59	1892	30 (1.59)	24 (1.27)	1725	33 (1.91)	41 (2.38)
60+	2720	42 (1.54)	49 (1.80)	2483	42 (1.69)	46 (1.85)
Total†	**12 928**	**139** (1.08)	**143** (1.11)	**12 058**	**153** (1.27)	**165** (1.37)

*XN indicates history of night blindness; X1B, presence of Bitot's spots as independent criteria.

†Includes three UNIVAC (universal distribution program) and 13 TARVAC (targeted distribution program) children whose ages were unknown.

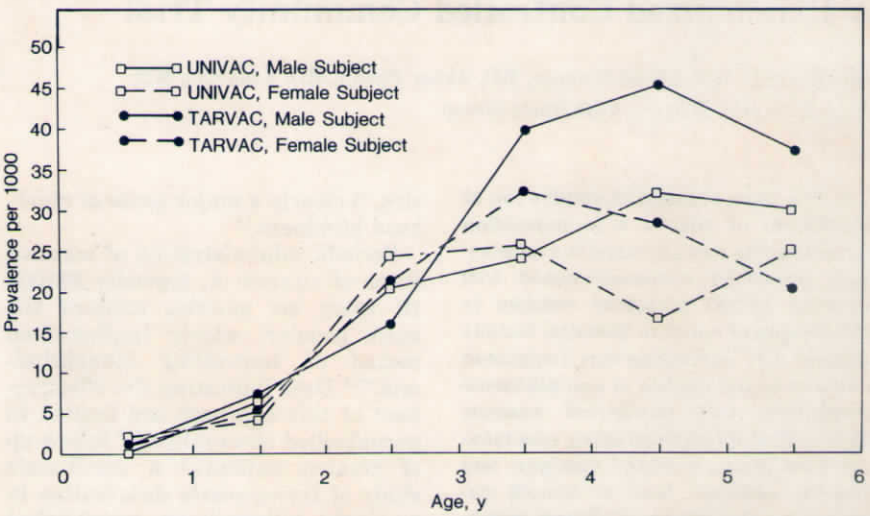

Fig 1.—Baseline age-specific prevalence of active xerophthalmia (night blindness, Bitot's spots, and/or corneal ulceration) among preschool children in UNIVAC (universal distribution program) and TARVAC (targeted distribution program) villages, Aceh, Indonesia.

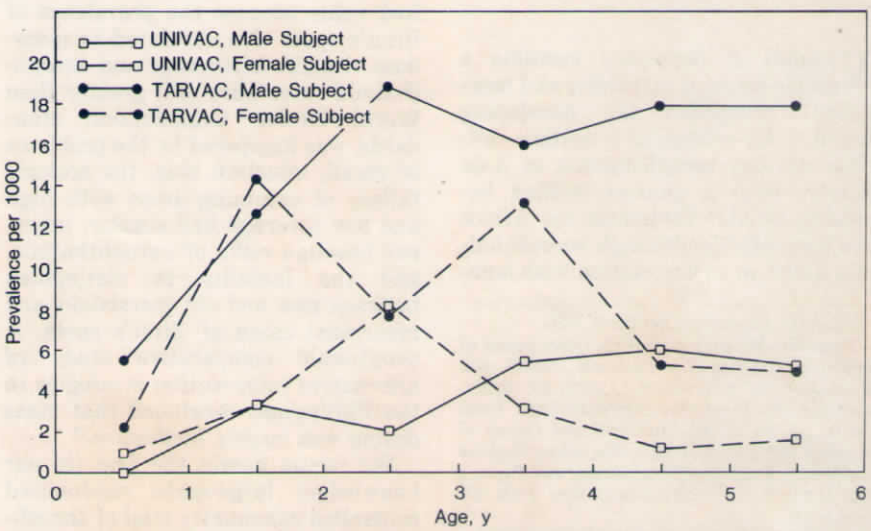

Fig 2.—Follow-up prevalence of new cases of active xerophthalmia among preschool children in UNIVAC (universal distribution program) and TARVAC (targeted distribution program) villages, Aceh, Indonesia. Age is same at baseline examination.

Table 2.—Age-Specific Rate of New Cases of Xerophthalmia at Follow-up Examination*

Age, mo	Program (UNIVAC) Villages			Control (TARVAC) Villages		
	No. of Children	XN, No. (%)	X1B, No. (%)	No. of Children	XN, No. (%)	X1B, No. (%)
0-11	1990	1 (0.05)	0 (0.00)	1887	3 (0.16)	4 (0.21)
12-23	1903	6 (0.32)	3 (0.16)	1874	17 (0.91)	14 (0.75)
24-35	2027	7 (0.35)	2 (0.10)	1990	21 (1.06)	6 (0.30)
36-47	2203	5 (0.23)	3 (0.14)	1996	16 (0.80)	17 (0.85)
48-59	1830	4 (0.22)	2 (0.11)	1672	11 (0.66)	8 (0.48)
60+	2635	4 (0.15)	3 (0.11)	2384	15 (0.63)	10 (0.42)
Total†	**12 591**	**27** (0.21)	**13** (0.10)	**11 818**	**83** (0.70)	**59** (0.50)

*XN indicates history of night blindness; X1B, presence of Bitot's spots as independent criteria. Excludes 386 children with xerophthalmia and/or vitamin A receipt at baseline examination.

†Includes three UNIVAC (universal distribution program) and 15 TARVAC (targeted distribution program) children whose ages were unknown.

Table 3.—Relative Risk (RR) of Xerophthalmia*

	Baseline		New Cases at Follow-up	
	RR	$CL_{95\%}$†	RR	$CL_{95\%}$†
XN	1.2	(0.8, 1.8)	3.3	(1.9, 5.7)
X1B	1.2	(0.8, 1.9)	5.0	(2.3, 10.9)
XN, X1B, X3	1.2	(0.8, 1.7)	3.3	(2.2, 5.0)

*Prevalence rate in TARVAC (targeted distribution program) villages divided by prevalence rate in UNIVAC (universal distribution program) villages. XN indicates night blindness; X1B, Bitot's spot as independent criteria; X3, xerophthalmic ulceration; XN, X1B, X3, as mutually exclusive criteria.

†Confidence limits (CL) adjusted for design effect calculated by applying poisson regression with extrapoisson variation to account for natural variability in xerophthalmia rates among villages. The design effect at baseline was conservatively estimated at 3.5, and at follow-up (of new cases) at 1.4.

Table 4.—Prevalence of Bitot's Spots (X1B) at Follow-up in Relation to Bitot's Spot Status at Baseline*

	No Bitot's Spot at Baseline		Bitot's Spot at Baseline	
	No. of Children	X1B, No. (%)	No. of Children	X1B, No. (%)
UNIVAC villages	12 277	15 (0.12)	140	20 (14.3)
TARVAC villages	11 342	55 (0.48)	160	20 (12.5)

*Results limited to children examined both at baseline and follow-up. UNIVAC indicates universal distribution program of vitamin A; TARVAC, targeted distribution program.

TARVAC children, 12 928 and 12 058, respectively. The age-specific prevalence of night blindness and of Bitot's spots was similar, rising rapidly from the first to third years of life (Table 1). There were only four cases of xerophthalmic ulceration among UNIVAC children and three among TARVAC children. The rate of active xerophthalmia (night blindness, Bitot's spots, and/or xerophthalmic ulceration as mutually exclusive criteria) was higher among TARVAC than UNIVAC children at baseline, 2.14% vs 1.81%, respectively ($P < .05$). Excess xerophthalmia in control villages was confined to older children, predominantly boys (Fig 1).

Excluding children who received vitamin A at the baseline examination, 93.2% of UNIVAC children reportedly received at least one capsule and 78.1% two capsules from village distributors.[3] Only 1.1% of TARVAC children of the same age reportedly received any capsules and 0.2% received two capsules, presumably when presenting to health centers with active xerophthalmia. A larger proportion of infants in UNIVAC villages received capsules than were eligible under government guidelines: 82.4% received at least one capsule and 61.8% received two capsules, vs 1.1% and 0.1% in TARVAC villages.[3] Coverage rates in UNIVAC villages, therefore, reached target levels.

Ninety-six percent of UNIVAC and TARVAC study cohorts were examined at follow-up, one year later. The prevalence of new cases of active xerophthalmia (eg, among those free of xerophthalmia or receipt of vitamin A at baseline examination) was 0.33% (42/12 588) in UNIVAC villages and 1.10% (130/11 803) in TARVAC villages, a decline of 82% and 49%, respectively. Almost all the reduction in xerophthalmia prevalence occurred among the older age groups (Table 2, Fig 2), in whom baseline rates were highest to begin with.

The degree of impact varied with the clinical indicator. Between baseline and follow-up, the relative risk of night blindness in TARVAC vs UNIVAC villages increased from 1.2 to 3.3, while for Bitot's spots it increased from 1.2 to 5.0 (Table 3).

The follow-up prevalence rate of night blindness among all study children from UNIVAC villages, regardless of ocular status or treatment at baseline, was only 15% to 20% greater than the prevalence rate of new cases. The follow-up prevalence of Bitot's spots in UNIVAC villages, however, was almost 200% greater than the prevalence rate of new cases, reflecting the impact distribution had on new disease but not on the persistence or recurrence of Bitot's spots among children with previous disease. Bitot's spots were 30 to 100 times more frequent at follow-up among children with Bitot's spots at baseline than among children originally free of disease (Table 4).

COMMENT

The Aceh (Indonesia) study provides a unique opportunity for evaluating the effectiveness of periodic mass-dose vitamin A supplementation in reducing the risk of xerophthalmia. Being a large-scale, randomized, longitudinal, concurrently controlled trial, it avoids many of the limitations of earlier investigations, especially those employing indirect indicators of outcome.[20] It also permits comparison with conclusions that have been reached through retrospective and case-control analyses of point prevalence surveys. Coverage rates were comparable with those reported from other regions, although in usual practice these fall with succeeding distribution cycles.[10,11]

Baseline xerophthalmia rates were slightly (and not statistically) higher in TARVAC than UNIVAC villages. Prevalence rates rose rapidly during the first two to three years of life and were higher in boys, consistent with observations elsewhere.[6,7,16,20,21]

Prevalence rates at follow-up, one year later, were dramatically lower in both groups of villages, proving the

Table 5.—Prevalence of Xerophthalmia in Relation to Capsule Receipt

	Prevalence of Xerophthalmia (Night Blindness and Bitot's Spots)			
	Bangladesh[15,16]		Present Study	
	Capsule Not Received	Capsule* Received	Capsule Not Received	Capsule† Received
XN, No. (%)	. . . (4.4)	. . . (2.6)	4/656 (0.61)	22/9484 (0.23)
Relative risk	1.9	1	2.7	1
X1B, No. (%)	. . . (9.8)	. . . (8.2)	1/656 (0.15)	11/9484 (0.12)
Relative risk	1.3	1	1.3	1

*History of capsule receipt within the past six months.
†History of receiving one or more capsules during the past ten months.

necessity of concurrent controls for accurate quantification of programmatic impact. Overall, the prevalence in TARVAC villages fell by 49%. This "spontaneous" decline is probably attributable, in part, to the following: historical trends (baseline rates in Aceh were lower than recorded only three years previously,[6] a similar phenomenon being noted throughout many areas of Indonesia [Robert Tilden, MPH, and Dr Muhilal, PhD, oral communication, October 1982]); treatment of (high-risk) children with evidence of xerophthalmia at baseline examination; and the TARVAC approach of sensitizing health center staff to recognize and treat clinical diseases.

Rates did not decline among the youngest controls, presumably because the cohort had aged by one year. Those who had been infants at baseline, and therefore at low risk of xerophthalmia, were in an older, higher-risk category at follow-up.

The decline in prevalence rates in UNIVAC villages was even more dramatic and was present at every age. The apparent size of the decline and degree of impact depended on the clinical criterion. The prevalence of (new) cases of "active" xerophthalmia (night blindness, Bitot's spots, and/or corneal ulceration) in UNIVAC villages fell by 82% compared with the spontaneous fall in TARVAC villages of 49%. The relative risk of night blindness among TARVAC vs UNIVAC children rose from 1.2 at baseline to 3.3 at follow-up, a smaller change than for Bitot's spots (1.2 to 5.0). There may be a natural limit to the apparent reduction in night blindness rates detectable in routine surveys. Experience indicates that a properly elicited history of night blindness in endemically vitamin A–deficient populations can be a sensitive and specific index of vitamin A status.[6,19] As true prevalence declines, however, the positive predictive value (proportion of all positive histories that represents true cases) falls as well. It is also possible that we witnessed a shift in the severity curve to less prevalent as well as to milder expressions of deficiency.

Sinha and Bang[13] found that 100 000 IU of vitamin A every four months prevented development of Bitot's spots in children previously free of disease but that Bitot's spots recurred, despite prophylaxis, in children who had had Bitot's spots. It is likely that these cases represent localized areas of persistent epithelial metaplasia, largely unresponsive to vitamin A.[22,23] In this study, children with Bitot's spots at baseline had many times the rate of Bitot's spots at follow-up than did other children, despite receiving a therapeutic dose of vitamin A (200 000 IU) at baseline. The rate of recurrent or persistent Bitot's spots was identical in UNIVAC and TARVAC villages, indicating the importance of excluding such cases in evaluating program impact. This no doubt explains much of the apparent lack of program efficacy for Bitot's spots reported from Bangladesh.[16]

Intervention programs rarely have the luxury of recording baseline values, let alone randomized concurrently controlled data, against which their performance can be gauged. Ingenious indirect measures of impact have been suggested, most notably a flattening of the age-related rise in prevalence rates.[20] Such a change was noted in this study, moreso among UNIVAC than TARVAC villages. This finding provides support, in a different country and environment, for the value of this indirect indicator. By itself, however, it does not quantify the degree of improvement, since patterns of age-specified prevalence vary, nor does it permit attribution to the intervention itself.

Impact of capsule distribution in Bangladesh was assessed by comparing capsule receipt status with the presence of xerophthalmia in data from a countrywide prevalence survey.[15,16] Night blindness was only half as frequent among children reporting recent receipt of a vitamin A capsule. The difference in prevalence of Bitot's spots was much smaller. Interpretation of these results is complicated by the self-selection bias involved in choosing to accept a capsule. Those who participate in a program, by receiving a capsule, may differ in many ways (including intrinsic risk of xerophthalmia) from those who do not.[24] For similar reasons, 90% coverage will not necessarily result in an equivalent reduction in xerophthalmia rates: the 10% missed may contain a disproportionate share of all children at risk of disease. Retrospective case-control analyses in Bangladesh and this study yield comparable results (Table 5); in our study, however, the direct technique of comparing baseline with follow-up rates of disease for UNIVAC and TARVAC areas demonstrated that the real degree of programmatic impact was much greater.

In our study and the Bangladesh study[16] some children who reportedly recently received a capsule still had xerophthalmia. In part this may reflect reporting error, in part a residuum of disease in a subset of children with such severe contributory factors (diet, diarrhea, etc) that a single capsule once every six months is inadequate for prevention of (mild) xerophthalmia.[25]

Our study demonstrates that an enormous reduction in disease (82%) is consistent with apparently less dramatic results obtained through a variety of retrospective techniques, that almost half of this reduction may have been spontaneous, and that the choice of clinical indicators will determine, to varying degrees, the apparent level of benefit.

This study was unable to evaluate the effectiveness of periodic massive dosing in preventing corneal ulceration. The study area had been specifically selected for the high rate of active corneal xerophthalmia (night blindness, xerophthalmic ulceration) and xerophthalmic scarring recorded three years previously.[6] Fortunately for the population (and for reasons that remain obscure), the rates had fallen precipitously in the interim. Recent data from India[26] and indirect analyses from Bangladesh,[16] however, provide indirect evidence that high coverage rates may be associated with reduced risk of blindness.

Periodic massive-dose vitamin A supplementation is far from an ideal solution to the problem of vitamin A

deficiency and xerophthalmia. While the capsules are inexpensive, provision is costly and logistically difficult, coverage declines with the drop in enthusiasm accompanying successive rounds, and the children who need the capsule most are probably least likely to receive it.[10,16,24] It was begun as an "emergency, short-term" measure. Unfortunately it remains the predominant intervention strategy and will remain so until fortification and nutrition education take root. It is encouraging to have this additional assurance that mass dosing is effective. The insights provided by this attempt at measuring clinical impact should prove equally relevant to assessing the value of alternative intervention strategies.

This investigation was carried out under cooperative agreement DSAN-CA-0267 between the International Center for Epidemiologic and Preventive Ophthalmology and the Office of Nutrition, US Agency for International Development, State Department, Washington, DC, with additional financial support from Task Force Sight and Life of Hoffman-La Roche, Basel, Switzerland; P. T. Vicks, Indonesia; Ford Foundation, New York and Jakarta; United Nations Children's Fund; and the Asian Foundation for the Prevention of Blindness, Hong Kong.

The Aceh Study Group includes the following professional staff, apart from the authors: A. A. Loeden, MD, PhD; Keith P. West, Jr, Dr PH; Barbara Hawkins, MS; Ignatius Tarwotjo, MSC; Lisa Mele, MS; Robert Tilden, MPH; Daniel Kraushaar, Dr PH; and William Flumenbaum, MA.

References

1. Sommer A, Katz J, Tarwotjo I: Increased risk of respiratory disease and diarrhea in children with preexisting mild vitamin A deficiency. *Am J Clin Nutr* 1984;40:1090-1095.

2. Sommer A, Tarwotjo I, Hussaini G, et al: Increased mortality in mild vitamin A deficiency. *Lancet* 1983;2:585-588.

3. Sommer A, Tarwotjo I, Djunaedi E, et al: Impact of vitamin A supplementation on childhood mortality: A randomised controlled community trial. *Lancet* 1986;1:1169-1173.

4. Muhilal, Soekirman: Dimensi baru dampak program penanggulangan defisiensi vitamin A: Penurunan angka kaskitan dan kematian pada anaka balita. *J Indonesia Nutr Assoc* 1986;11:1-6.

5. Sommer A, Tarwotjo I, Hussaini G: Incidence, prevalence and scale of blinding malnutrition. *Lancet* 1981;1:1407-1408.

6. Sommer A: *Nutritional Blindness: Xerophthalmia and Keratomalacia.* New York, Oxford University Press Inc, 1982.

7. Tielsch J, West KP, Katz J, et al: Prevalence and severity of xerophthalmia in southern Malawi. *Am J Epidemiol* 1986;124:561-568.

8. Sauter JJM: *Xerophthalmia and Measles in Kenya.* Groningen, the Netherlands, Drukkerij Van Denderen, 1976.

9. Foster A, Sommer A: Corneal ulceration, measles and childhood blindness in Tanzania. *Br J Ophthalmol* 1987;71:331-343.

10. West KP Jr, Sommer A: *Periodic Large Oral Doses of Vitamin A for the Prevention of Vitamin A Deficiency and Xerophthalmia: A Summary of Experiences.* Washington, DC, IVACG Report, Nutrition Foundation, 1984.

11. Report of a Joint WHO/UNICEF/USAID/HKI/IVACG Meeting: *Control of Vitamin A Deficiency and Xerophthalmia.* Technical report series 672. Geneva, World Health Organization, 1982.

12. Swaminathan MC, Susheela TP, Thimmayamma BVS: Field prophylactic trial with a single annual oral massive dose of vitamin A. *Am J Clin Nutr* 1970;23:119-122.

13. Sinha DP, Bang FB: The effect of massive doses of vitamin A on the signs of vitamin A deficiency in preschool children. *Am J Clin Nutr* 1976;29:110-115.

14. Tarwotjo I, ten Doesschate J, Gunawan S, et al: *An Evaluation of the Vitamin A Deficiency Prevention Pilot Project in Indonesia.* New York, American Foundation for Overseas Blind, 1976.

15. Cohen N, Rahman H, Sprague J, et al: Prevalence and determinants of nutritional blindness in Bangladeshi children. *World Health Stat Q* 1985;38:317-330.

16. Cohen N, Rahman H, Mitra M, et al: Impact of massive doses of vitamin A on nutritional blindness in Bangladesh. *Am J Clin Nutr* 1987;45:970-976.

17. Solon F, Fernandez TL, Latham MC, et al: An evaluation of strategies to control vitamin A deficiency in the Philippines. *Am J Clin Nutr* 1979;32:1445-1453.

18. Sommer A: *Field Guide to the Detection and Control of Xerophthalmia,* ed 2. Geneva, World Health Organization, 1982.

19. Sommer A, Hussaini G, Muhilal, et al: History of night blindness: A simple tool for xerophthalmia screening. *Am J Clin Nutr* 1980;33:887-891.

20. Vijayaraghavan K, Naider AN, Rao NP, et al: A simple method to evaluate the massive dose vitamin A prophylaxis program in preschool children. *Am J Clin Nutr* 1975;29:1189-1193.

21. Brilliant LB, Pokhrel RP, Grasset NC, et al: Epidemiology of blindness in Nepal. *Bull WHO* 1985;63:375-386.

22. Sommer A, Emran N, Tjakrasudjatma S: Clinical characteristics of vitamin A responsive and nonresponsive Bitot's spots. *Am J Ophthalmol* 1980;90:160-171.

23. Sommer A, Green WR, Kenyon KR: Bitot's spots responsive and nonresponsive to vitamin A: Clinicopathologic correlations. *Arch Ophthalmol* 1981;99:2014-2027.

24. Tarwotjo I, Sommer A, West KP, et al: Influence of participation on mortality in a randomized trial of vitamin A prophylaxis. *Am J Clin Nutr* 1987;45:1466-1471.

25. Periera SM, Begum A: Failure of a massive dose of vitamin A to prevent deficiency. *Arch Dis Child* 1971;46:525-527.

26. Vijayaraghavan K, Sarma KVR, Rao NP, et al: Impact of massive doses of vitamin A on incidence of nutritional blindness. *Lancet* 1984;2:149-151.

Printed and Published in the United States of America