

Vitamin A Supplementation and Child Mortality

A Meta-analysis

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Objective.—A two-part meta-analysis of studies examining the relationship of vitamin A supplementation and child mortality.

Data Sources.—We identified studies by searching the MEDLARS database from 1966 through 1992 and by scanning *Current Contents* and bibliographies of pertinent articles.

Study Selection.—All 12 vitamin A controlled trials with data on mortality identified in the search were used in the analysis.

Data Extraction.—Data were independently extracted by two investigators who also assessed the quality of each study using a previously described method.

Data Synthesis.—We formally tested for heterogeneity across studies. We pooled studies using the Mantel-Haenszel and the DerSimonian and Laird methods and adjusted for the effect of cluster assignment of treatment groups in community-based studies. Vitamin A supplementation to hospitalized measles patients was highly protective against mortality (DerSimonian and Laird odds ratio, 0.39; 95% confidence interval, 0.22 to 0.66; $P=.0004$) (part 1 of the meta-analysis). Supplementation was also protective against overall mortality in community-based studies (DerSimonian and Laird odds ratio, 0.70; clustering-adjusted 95% confidence interval, 0.56 to 0.87; $P=.001$) (part 2 of the meta-analysis).

Conclusions.—Vitamin A supplements are associated with a significant reduction in mortality when given periodically to children at the community level. Factors that affect the bioavailability of large doses of vitamin A need to be studied further. Vitamin A supplements should be given to all measles patients in developing countries whether or not they have symptoms of vitamin A deficiency.

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VITAMIN A deficiency is a major public health problem in many developing countries. Five to 10 million children exhibit eye signs of vitamin A deficiency and 10 times as many may experience subclinical depletion of vitamin A.¹ The relationship between vitamin A deficiency and child mortality was noted as early

as the 1930s when supplementation with vitamin A was reported to significantly reduce mortality among measles patients.² A number of cross-sectional and observational studies in the last three decades have shown an association between xerophthalmia and higher levels of mortality.³ More recently, a number of controlled trials have been conducted to investigate further the relationship of vitamin A supplementation and child mortality. However, the evidence provided has been inconsistent. The objective of this article is to provide a meta-analysis of the published controlled trials in this area. Hospital-based

studies of measles patients (part 1) and community-based studies (part 2) were examined in this analysis.

METHODS

Controlled trials were identified by searching the Medical Literature Analysis and Retrieval System (MEDLARS, National Library of Medicine, Bethesda, Md) database from 1966 through 1992 using a number of key words including *vitamin A*, *clinical trials*, *measles*, and *child mortality*, by scanning *Current Contents* for all clinical trials, and by reading the reference lists of those articles reporting the trials and other review papers. We identified 12 published controlled trials with data on child mortality^{2,4-14} and used all of them in the analysis.

We assessed the quality of each trial using a previously described method that evaluates a study's design, implementation, and analysis.¹⁵ Each study was scored by two investigators, one of whom was blinded to the names of the authors, journal, dates of studies, treatment groups, study site, and results. There was a discrepancy in 51 (15%) of 341 items in the quality assessment of the 12 studies, 9% owing to investigator error and 6% owing to differences in judgment. Discrepant items were discussed and a final score was assigned for each study. We used the scores in sensitivity analyses whereby studies of lower quality were removed from the pool to examine their effect on the pooled estimate and confidence interval (CI).¹⁶

The 12 studies, listed in Table 1, are divided into the two parts of our meta-analysis. Each part also involved a number of subgroup analyses.

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Table 1.—Hospital- and Community-Based Controlled Trials of Vitamin A Supplementation

Quality Score	Location of Trial, Year	Experimental Regimen*	Controlled Regimen*	Treatment Unit, No.	Observers Blinded?
Hospital-Based Studies					
1	Cape Town, South Africa, 1990 ⁴	420 $\mu\text{mol/L}$ (400 000 IU) vitamin A; half on admission, half next day	Placebo	Individuals, 189†	Yes
2	Tanzania, 1988 ⁵	420 $\mu\text{mol/L}$ (400 000 IU) vitamin A; half on admission, half next day	No placebo	Individuals, 186†‡	No
3	Durban, South Africa, 1991 ⁶	210 $\mu\text{mol/L}$ (200 000 IU) vitamin A on admission, days 2 and 8	Placebo	Individuals, 60†	Yes
4	London, England, 1932 ²	300 Carr and Price units vitamin A§ and 2000 IU vitamin D§ daily for 7-21 d	No placebo	Individuals, 600	No
Community-Based Studies					
1	Sarlahi, Nepal, 1991 ⁷	210 $\mu\text{mol/L}$ (200 000 IU) vitamin A, 92 $\mu\text{mol/L}$ (40 IU) vitamin E per 4 mo	1 $\mu\text{mol/L}$ (1000 IU) vitamin A, 92 $\mu\text{mol/L}$ (40 IU) vitamin E per 4 mo	Wards, 261†	Yes
2	Northern Sudan, 1992 ⁸	210 $\mu\text{mol/L}$ (200 000 IU) vitamin A, 92 $\mu\text{mol/L}$ (40 IU) vitamin E per 6 mo	92 $\mu\text{mol/L}$ (40 IU) vitamin E per 6 mo	Households, 16789†	Yes
3	Tamil Nadu, India, 1990 ⁹	87 $\mu\text{mol/L}$ (8333 IU) vitamin A, 46 $\mu\text{mol/L}$ (20 mg) vitamin E in peanut oil per wk	46 $\mu\text{mol/L}$ (20 mg) vitamin E in peanut oil per wk	Clusters, 206†	Yes
4	Aceh, Indonesia, 1986 ¹⁰	210 $\mu\text{mol/L}$ (200 000 IU) vitamin A, 92 $\mu\text{mol/L}$ (40 IU) vitamin E per 6 mo	No placebo	Villages, 450†	No
5	Hyderabad, India, 1990 ¹¹	210 $\mu\text{mol/L}$ (200 000 IU) vitamin A in peanut oil per 6 mo	Peanut oil placebo per 6 mo	Villages, 84†	Yes
6	Jumla, Nepal, 1991 ¹²	210 $\mu\text{mol/L}$ (200 000 IU) vitamin A once	No placebo	Districts, 16†	No
7	Java, Indonesia, 1988 ¹³	2.8 $\mu\text{mol/L}$ (810 retinol equivalents) per g of MSG in diet	Unfortified MSG	Areas, 2	No
8	Bombay, India, 1991 ¹⁴	210 $\mu\text{mol/L}$ (200 000 IU) vitamin A once	No placebo	Slums, 2	No

*Half the dose was given to infants 6 to 11 months of age and one-quarter the dose to infants up to 6 months of age.

†Random assignment of treatments.

‡Six children were excluded after randomization.

§Equivalent SI units unknown.

||MSG indicates monosodium glutamate.

Part 1 of the meta-analysis was conducted on hospital-based studies. We carried out a primary analysis examining the relationship of vitamin A supplementation and mortality from measles using four hospital-based studies. We secondarily examined the effect of vitamin A on mortality due to pneumonia among the total number of patients as well as among patients who were sick with pneumonia. We also conducted subanalyses within age categories.

Part 2 of the meta-analysis was conducted on community-based studies. We primarily examined the relationship of vitamin A supplementation to total mortality using eight community-based studies. We performed secondary subanalyses, stratifying by dose of vitamin A, age, gender, and risk of mortality in the control group, and examined the relationship of vitamin A to cause-specific mortality.

The subgroup analyses were in part post hoc research. The CIs and *P* values are given for descriptive purposes only. These are useful for designing future studies, but because of their nonexperimental nature they cannot be accepted as conclusive. We used weighted least-squares regression to test for trend of the relationship in the dose subanalyses, weighing each category by the inverse of its variance. We also compared the odds ratios (ORs) and risk differences of a number of strata using Student's *t* test.

In a few instances, data for the subanalyses had to be derived from the re-

sults provided in the respective papers. In two studies mortality rates were reported,^{7,12} while in the other studies counts were used in the calculation of the measure of association. We derived counts for the former two studies from the description of the populations at baseline. This may have carried a small margin of error in the age subanalyses; however, this should not bias the results with respect to the effect of supplementation because both experimental and control groups were treated similarly. We used the intention-to-treat analysis with each study and assessed heterogeneity across studies.¹⁷ The combined results were calculated by two methods: the Mantel-Haenszel method,¹⁷ which takes account of within-study variance as affected by the size of the study sample but assumes homogeneity of the effect between studies (a fixed-effects model), and the DerSimonian and Laird method,¹⁸ which factors in both within-study variance as well as heterogeneity between studies, ie, between-study variance (a random-effects model). Odds ratios were calculated so that a value less than 1.00 indicates a protective association of the supplement. Similarly, a negative risk difference implies a protective relationship.

None of the eight community trials assigned individual children to treatment groups; rather, villages, districts, or households were assigned to vitamin A or control groups as outlined in Table 1. Only four of the studies adjusted for clustering effects resulting from this de-

sign.^{7,9,10,12} In these studies the increase in variance of the OR (in the log scale) as a result of adjustment ranged from about 10%⁷ to about 44%.¹² Since only half of the studies supplied information necessary to calculate a correction for the clustering effect, we chose to adjust for this by increasing the variance of any pooled OR (in the log scale) by a conservative 30%. This adjustment was applied to the DerSimonian and Laird CI. All *P* values are two-sided.

RESULTS

Part 1: Hospital-Based Measles Studies

The risk of mortality among the control groups of the hospital-based measles studies (Table 2) ranged from 3% to 13%. The four studies were not heterogeneous (χ^2 , 1.08; *df*, 3; *P* = .78) (Table 3). Overall, the studies showed a protective association with a Mantel-Haenszel OR of 0.37 (95% CI, 0.21 to 0.64; *P* = .0004) (Table 3). As expected, the corresponding DerSimonian and Laird pooled estimate was not appreciably different given the lack of heterogeneity of the studies (OR, 0.39; 95% CI, 0.22 to 0.66; *P* = .0004). The four studies provided a DerSimonian and Laird risk difference of -53.0 per 1000 patients (95% CI, -80.8 to -25.2; *P* = .0002) (Table 3). Removing the 1932 study,² which had a relatively weak design, did not change the OR much but widened the CI (Mantel-Haenszel OR, 0.33; 95% CI, 0.15 to 0.77).

Deaths related to respiratory infec-

tion accounted for approximately 80% of total mortality in the four studies. Examining this as an end point among the total number of patients provided a Mantel-Haenszel OR of 0.37 (95% CI, 0.20 to 0.69) (Table 3). Moreover, when the same end point (ie, pneumonia-specific mortality) was examined only among patients who had developed respiratory infection before or during their hospital stay, vitamin A supplementation was still significantly protective (Table 3). The protective effect of supplementation on all-cause mortality was highest within the first year of life. There was also a significantly protective relationship in the age group 12 to 23 months, and a protective, though not statistically significant, relationship among children 2 years of age or older (Table 3).

Part 2: Community-Based Studies

Table 4 lists mortality data on the children in the community-based trials

of vitamin A supplementation. Two of the studies had an OR of 1.00 or close to 1.00 (Figure)^{8,11}; however, combined analysis of the eight studies using the Mantel-Haenszel method provided an OR of 0.72 (95% CI, 0.66 to 0.79) (Table 5). Given that the eight studies were heterogeneous in terms of their effect estimates ($P=.0004$), we also pooled the studies using the DerSimonian and Laird method (which allows for heterogeneity between studies) and obtained an OR of 0.70 (95% CI, 0.58 to 0.85) (Table 5). Removal of the lowest one and then the lowest two studies according to the quality score did not appreciably change the results. On further adjusting for the clustering effect, the CIs were widened as expected but did not include 1.00 (ie, the relationship retained its statistical significance). The top six studies in terms of quality provided a DerSimonian and Laird OR of 0.75 (clustering-adjusted 95% CI, 0.59 to 0.95; $P=.02$) (Table 5).

We next examined the relationship of vitamin A supplementation and child mortality within subgroups of potential modifiers of this relationship, for which we reported the clustering-adjusted DerSimonian and Laird results (Table 6). Children receiving either small frequent doses or large doses of vitamin A every 4 to 6 months experienced a statistically significant reduction in mortality compared with control children. The protective relationship seemed to be stronger with small frequent doses (OR, 0.58) compared with large periodic doses (OR, 0.81); however, the difference in performance was not statistically significant ($z=1.26$; $P=.21$). We noted a gradual increase in the protective relationship with each large dose given every 4 to 6 months after the first with the effect of the third dose reaching statistical significance; however, a test for trend over doses was not significant at the .05 level ($P=.13$). Pooling the three studies that used the large dose every 6 months provided a small protective association that was no longer statistically significant ($P=.46$) (Table 6).

The protective effect of vitamin A supplements on mortality was more evident among younger children but there was no particular trend over the different age categories. The ages used in these analyses were the ages at dosing and not those at the end of each study. We could not examine the effect of vitamin A supplementation on infant mortality. Boys and girls experienced a comparable reduction in mortality associated with vitamin A supplementation.

The annual risk of mortality among the control groups of the eight community-based studies ranged from about 0.5% to 12%. We stratified the studies using this risk into a low-risk group (ranging from 0.5% to 1.5%) and a high-risk group (two studies with annual risk of about 4.6% and 11.8%). We noted comparable mortality ORs in study areas with high or low risk of mortality ($z=0.41$; $P=.68$). In absolute terms, however, a

Table 2.—Vitamin A Supplementation and Hospital Mortality Among Children With Measles*

Quality Score	Trial	No. of Deaths/Total		Odds Ratio (95% CI)†	Risk Difference per 1000 Children (95% CI)
		Vitamin A	Control		
1	Cape Town, South Africa ⁴	2/92	10/97	0.19 (0.04 to 0.91)	-81.4 (-148.8 to 13.9)
2	Tanzania ⁵	6/88	12/92	0.49 (0.17 to 1.36)	-62.3 (-148.9 to 24.4)
3	Durban, South Africa ⁶	0/29	1/31	0.34 (0.01 to 8.80)	-32.3 (-94.5 to 29.9)
4	London, England ²	11/300	26/300	0.40 (0.19 to 0.83)	-50.0 (-88.3 to -11.7)

*Studies arranged by descending quality score.

†CI indicates confidence interval.

Table 3.—Vitamin A Supplementation and Hospital Mortality Among Children With Measles, in Pooled Studies

	Studies Pooled*	Total No. of Subjects	Homogeneity, χ^2 , df, P	Mantel-Haenszel OR (95% CI)†	P
All-cause mortality	1-4	1029	1.08, 3, .78	0.37 (0.21-0.64)	.0004
Pneumonia-specific mortality	1-4	1029	0.43, 3, .93	0.37 (0.20-0.69)	.002
Mortality among pneumonia patients	2, 4	151	1.76, 1, .18	0.29 (0.13-0.68)	.004
Mortality by age, mo					
0-11	1, 2, 4	232	0.55, 2, .76	0.12 (0.03-0.51)	.004
12-23	1, 2, 4	271	0.34, 2, .84	0.42 (0.19-0.94)	.03
≥24	1, 2, 4	466	1.70, 2, .43	0.63 (0.24-1.64)	.34

*Numbers for pooled studies correspond to quality scores in Table 2.

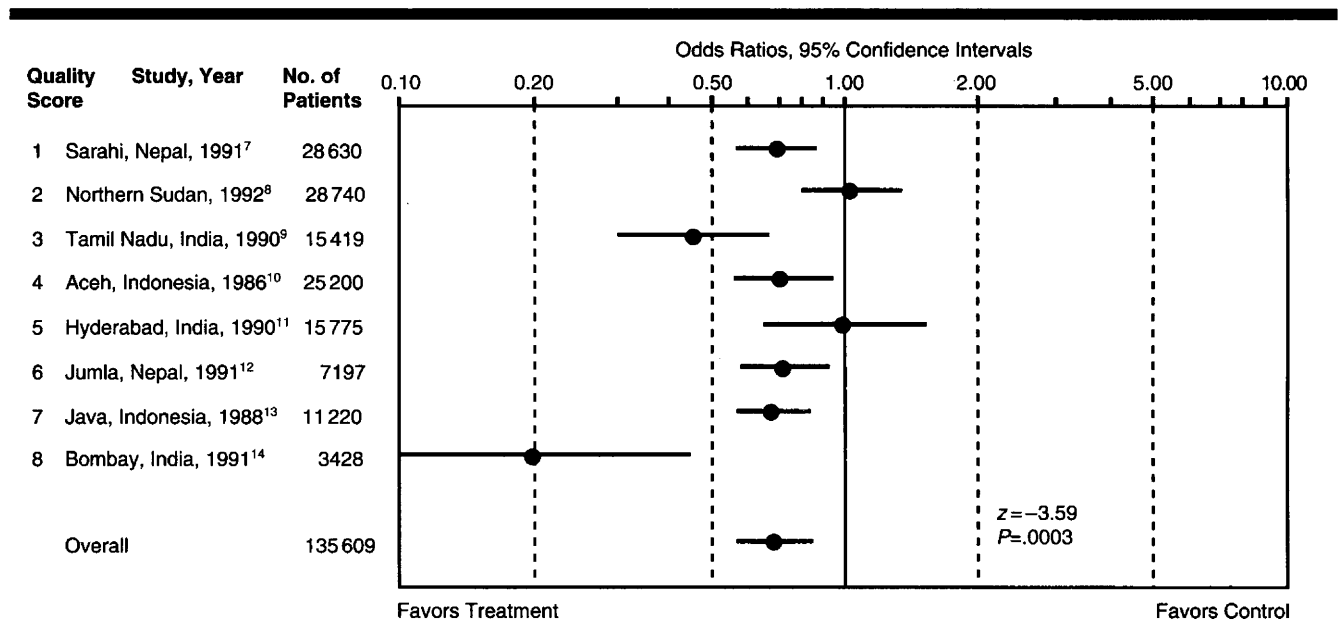
†OR indicates odds ratio; and CI, confidence interval. DerSimonian and Laird risk difference per 1000 children (pooling studies 1 through 4), -53.0; 95% CI, -80.8 to -25.2; $P=.0002$.

Table 4.—Mortality in Community-Based Trials of Vitamin A Supplementation in Children Aged 6 to 72 mo*

Quality Score	Location of Trial	Observation Period, mo	No. of Deaths/Total (Risk/1000 Children)		Odds Ratio (95% CI)†	Risk Difference per 1000 Children (95% CI)
			Vitamin A	Control		
1	Sarlahi, Nepal ⁷	12	152/14 487 (10.5)	210/14 143 (14.8)	0.70 (0.57 to 0.87)	-4.4 (-6.9 to -1.8)
2	Northern Sudan ⁸	18	123/14 446 (8.5)	117/14 294 (8.2)	1.04 (0.81 to 1.34)	0.3 (-1.8 to 2.4)
3	Tamil Nadu, India ⁹	12	37/7764 (4.8)	80/7655 (10.5)	0.45 (0.31 to 0.67)	-5.7 (-8.4 to -2.9)
4	Aceh, Indonesia ¹⁰	12	101/12 991 (7.8)	130/12 209 (10.6)	0.73 (0.56 to 0.95)	-2.9 (-5.2 to -0.5)
5	Hyderabad, India ¹¹	12	39/7691 (5.1)	41/8084 (5.1)	1.0 (0.64 to 1.55)	0 (-2.2 to 2.2)
6	Jumla, Nepal ¹²	5	138/3786 (36.5)	167/3411 (50.0)	0.73 (0.58 to 0.93)	-12.5 (-21.9 to -3.1)
7	Java, Indonesia ¹³	12	186/5775 (32.2)	250/5445 (45.9)	0.69 (0.57 to 0.84)	-13.7 (-20.9 to -6.5)
8	Bombay, India ¹⁴	42	7/1784 (3.9)	32/1644 (19.5)	0.2 (0.09 to 0.45)	-15.5 (-22.8 to -8.3)

*Studies arranged by descending quality score.

†CI indicates confidence interval.



Vitamin A supplementation and child mortality in community-based trials. Left, Studies are arranged by descending quality score. Right, Odds ratios (including 95% confidence intervals) of the studies (pooled using the DerSimonian and Laird method) are plotted; the *P* value is for a test of heterogeneity using the same method.

Table 5.—Mortality in Community-Based Trials of Vitamin A Supplementation in Children Aged 6 to 72 mo, in Pooled Studies

Studies Pooled*	Homogeneity, χ^2 , df, <i>P</i>	Mantel-Haenszel OR (95% CI)†	DerSimonian and Laird OR (95% CI)	DerSimonian and Laird OR (Clustering-Adjusted 95% CI), <i>P</i> ‡
1-8	26.81, 7, .0004	0.72 (0.66 to 0.79)	0.70 (0.58 to 0.85)	0.70 (0.56 to 0.87), .001
1-7	16.88, 6, .01	0.74 (0.67 to 0.81)	0.74 (0.63 to 0.87)	0.74 (0.62 to 0.89), .001
1-6	16.16, 5, .006	0.76 (0.68 to 0.84)	0.75 (0.62 to 0.92)	0.75 (0.59 to 0.95), .02

*Numbers for pooled studies correspond to quality scores in Table 4.

†OR indicates odds ratio; and CI, confidence interval.

‡DerSimonian and Laird risk difference (pooling studies 1 through 8), -5.1; 95% CI, -8.1 to -2.2; *P* = .0006.

significantly larger proportion of deaths was averted in the high-risk areas (DerSimonian and Laird risk difference, -13.3 per 1000; 95% CI, -19.0 to -7.6) compared with the low-risk areas (DerSimonian and Laird risk difference, -4.7 per 1000; 95% CI, -2.4 to -0.1) ($z=3.48$; $P=.0005$).

Diarrhea accounted for almost half of the deaths in the four studies that reported cause-specific mortality. Vitamin A supplementation was associated with about 30% reduction in the risk of diarrhea-specific mortality. There was a protective, though not statistically significant, relationship between vitamin A supplementation and measles-specific mortality, while the association with pneumonia-specific mortality was almost nil (Table 6).

COMMENT

This meta-analysis shows that vitamin A supplementation reduced mortality when given in addition to routine treatment of patients hospitalized with

measles as well as when given to children in the community. The possibility of publication bias needs to be considered whenever a positive result is found in any published study. Publication bias is impossible to rule out, but whenever the results are as positive as they are in this study, it is unlikely that publication bias is the source. Another potential source of bias is the inclusion of studies in which the patients or communities were not assigned at random. That was the case with one measles study² and two community-based studies.^{13,14} However, sensitivity analyses with these studies omitted did not change the results.

Combined analyses showed that massive doses of vitamin A given to patients hospitalized with measles (part 1) were associated with an approximate 60% reduction in the risk of death overall, and with an approximate 90% reduction among infants. Two of the four studies included in the hospital-based analyses were carried out among populations in which vitamin A deficiency is not a public health problem.^{4,6,19} Administration

of vitamin A to children who developed pneumonia before or during hospital stay reduced mortality by about 70% compared with control children. The latter finding suggests that vitamin A supplementation reduced the severity of pneumonia among these patients. This is in accord with the findings of studies that reported a reduced severity of pneumonia and diarrhea among measles patients who received vitamin A compared with children who received a placebo.^{4,6} Vitamin A supplementation in community-based studies was also associated with reduced risk of measles-related mortality.

Measles is responsible for about 1.5 million deaths worldwide every year.²⁰ Although prevention of measles through immunization is optimal, difficulties in procurement and distribution of the vaccine render millions of children unprotected against the virus. Vitamin A supplements should be given to all measles patients in developing countries whether they have symptoms of vitamin A deficiency or not, as recommended by the World Health Organization.²¹ Vitamin A may also protect measles patients in developed countries; a decreased serum retinol level was recently reported among American children with this disease compared with control children.^{22,23} More data are needed on the effects of vitamin A in measles patients in developed countries, though the necessary studies might not be feasible because of the shrinking base of nonvaccinated children.

Combined analysis of the community-

Table 6.—Effects of Vitamin A Supplementation on Mortality Among Subgroups in Community-Based Studies

Mortality Subgroup	Studies Pooled*	Total No. of Subjects	DerSimonian and Laird OR (Clustering-Adjusted 95% CI)†	P
Mortality with dose‡				
Small frequent doses	3, 7	26 639	0.58 (0.37 to 0.92)	.02
Large doses every 4-6 mo	1, 2, 4-6	105 542	0.81 (0.68 to 0.97)	.02
Large doses every 6 mo	2, 4, 5	69 715	0.90 (0.68 to 1.19)	.46
First large dose	1, 2	53 545	0.95 (0.59 to 1.54)	.83
Second large dose	1, 2	52 670	0.87 (0.48 to 1.58)	.65
Third large dose	1, 2	52 872	0.67 (0.47 to 0.95)	.02
Mortality by age, mo‡				
0-11	1, 2, 4, 6	13 949	0.73 (0.58 to 0.92)	.01
12-23	1, 2, 4, 6	16 865	0.90 (0.70 to 1.15)	.40
24-35	1, 2, 4, 6	16 477	0.89 (0.57 to 1.39)	.61
36-47	1, 2, 4, 6	16 139	0.94 (0.49 to 1.79)	.85
48-59	1, 2, 4, 6	15 359	0.80 (0.38 to 1.70)	.56
Mortality by gender				
Male	1-4, 6	51 908	0.75 (0.56 to 1.01)	.06
Female	1-4, 6	49 714	0.73 (0.56 to 0.95)	.02
Mortality by control group risk§				
Low	1-5	113 764	0.76 (0.58 to 1.00)	.05
High	6, 7	18 417	0.71 (0.60 to 0.84)	<.0001
Mortality by cause of death				
Diarrhea	1-3, 6	79 986	0.69 (0.57 to 0.84)	.01
Pneumonia	1-3, 6	79 986	0.96 (0.65 to 1.42)	.68
Measles	1-3, 6	79 986	0.61 (0.32 to 1.15)	.30

*Numbers of pooled studies correspond to quality scores in Table 4.

†OR indicates odds ratio; and CI, confidence interval.

‡Certain subanalyses were repeated with a larger number of studies but were not reported in the table to be able to compare categories using the same set of pooled studies; the DerSimonian and Laird odds ratios and clustering-adjusted 95% CIs are provided here. The first dose, including studies 4 and 6, provided an odds ratio of 0.84 (95% CI, 0.65 to 1.08); the second dose, including study 4, provided an odds ratio of 0.75 (0.46 to 1.22); the 0-through-11-month age category, including studies 3 and 7, provided an odds ratio of 0.76 (0.63 to 0.91). Pooling studies 2 and 4 for the effect among children 60 months of age and older provided an odds ratio of 0.55 (0.11 to 2.77).

§Low control-group annual risk ranged from 0.5% to 1.5%, while the two high-risk studies were about 4.6% and 11.8%.

based studies showed a significant reduction of mortality among children receiving vitamin A supplements compared with control children. We noted an increasingly protective effect with each additional large dose after the first. The investigators of a large community study carried out in Ghana found that the effect of four monthly large doses of vitamin A was consistent with a protective effect of vitamin A supplementation on mortality (relative rate, 0.81; 95% CI, 0.68 to 0.98) (David Ross, MD, written communication, November 1992). When we added these data to the pool of eight community-based studies, the results were not appreciably different (DerSimonian and Laird OR, 0.72; clustering-adjusted 95% CI, 0.60 to 0.87). We also obtained similar results when we included this new information in the pool with the six studies that had the highest quality scores ((DerSimonian and Laird OR, 0.77; 95% CI, 0.65 to 0.91).

The rationale behind periodic large doses of vitamin A is to replenish liver stores and thus prevent the occurrence of vitamin A deficiency in the period between doses. In this study, we noted a modest and nonsignificant reduction (about 10%) in mortality when we exclusively examined studies in which large

doses were given every 6 months. In contrast, identical doses given every 4 months⁷ or 5 months¹² were each associated with a significant reduction (about 30%) in mortality. The duration of protection provided by a large dose of vitamin A is affected by the bioavailability of the supplement, which in turn is a function of a number of variables. Decreased dietary fat intake,²⁴ intestinal infections, and parasitic infestations at the time of administration of the vitamin^{25,26} may interfere with the amount absorbed. Coexistent deficits of dietary zinc or dietary protein impair transport of vitamin A.²⁴ In addition, persistent infections (eg, diarrheal and respiratory infections) may increase the demand for vitamin A, resulting in faster depletion of body stores. The nutritional status (eg, as measured by anthropometric indexes) and the degree of depletion of vitamin A stores at the time of supplementation are probably important effect modifiers as well. The prevalence in different communities of a different set of modifiers and/or different levels within each factor may explain the heterogeneity in the effect of vitamin A supplementation noted between studies. These findings underscore the need to investigate factors that modify the ef-

fect of vitamin A supplements.

Although the overall effect of supplementation appeared to be greater among younger children, this was not the case in two studies in which older children benefited more from the supplements.^{7,10} The question of an effect of vitamin A supplementation on infant mortality cannot be answered by these data. We noted no differences in the effect of supplements among boys compared with girls. However, gender influences are expected and indeed noted in differential reduction in mortality in individual studies: the Aceh, Indonesia, study favored boys¹⁰ and the Tamil Nadu, India, study favored girls.⁹

The protective effects of vitamin A on mortality are probably mediated via protective effects against common childhood infections. Vitamin A is necessary for the differentiation of gastrointestinal and respiratory epithelia, thus maintaining these barriers to infection.²⁷ Vitamin A may also be necessary to enhance cellular and humoral immunity.²⁸ However, in some of the trials that showed protective effects of vitamin A supplementation on mortality, there were no protective effects on morbidity (respiratory and diarrheal diseases).^{29,30} This seeming paradox could be explained if vitamin A supplementation reduces severity but not incidence of infections, as is shown by a recent morbidity study from Ghana.³¹ The protective effect of vitamin A against severe and fatal diarrhea (diarrhea-specific mortality) obtained in this meta-analysis is also in keeping with this interpretation.

Large doses of vitamin A provide a potentially quick solution to the problem of vitamin A deficiency in areas of the world where this is a public health problem. Even though periodic large doses of vitamin A are beneficial, their use as the only approach to the problem of vitamin A deficiency has limitations.³² Vitamin A deficiency coexists with other nutrient deficits that are not addressed by the supplementation program. In addition, the effectiveness of this approach is limited to the duration of the program, and children who live in distant places and who probably need the supplement most may be difficult to reach.

Most communities in which vitamin A deficiency is a serious problem have abundant supplies of vegetables and fruits rich in carotenoid with provitamin A activity. The effectiveness of nutrition education programs in these communities should be examined in addition to the administration of supplements. In areas of the world where vitamin A-containing foods are not so abundant,

horticultural approaches should be considered. Vitamin A intervention strategies should be integrated into community programs dealing with other health problems rather than implemented as a vertical program.

CONCLUSIONS

Large doses of vitamin A are clearly lifesaving when given to children with measles. More research is needed to un-

derstand the effect of vitamin A as an adjuvant to conventional therapy in other serious childhood illnesses such as diarrheal and lower respiratory infections. Vitamin A supplements are also associated with a significant reduction in mortality when given periodically to children at the community level. Factors that affect the bioavailability of these large doses need to be studied further.

References

1. Underwood BA. Vitamin A prophylaxis programs in developing countries: past experiences and future prospects. *Nutr Rev*. 1990;48:265-274.
2. Ellison JB. Intensive vitamin therapy in measles. *BMJ*. 1982;2:708-711.
3. Sommer A. *Nutritional Blindness: Xerophthalmia and Keratomalacia*. Oxford, England: Oxford University Press; 1982.
4. Hussey GD, Klein M. A randomized, controlled trial of vitamin A in children with severe measles. *N Engl J Med*. 1990;323:160-164.
5. Barclay AJ, Foster A, Sommer A. Vitamin A supplements and mortality related to measles: a randomized clinical trial. *BMJ*. 1987;294:294-296.
6. Coutsooudis A, Broughton M, Coovadia HM. Vitamin A supplementation reduces measles morbidity in young African children: a randomized, placebo-controlled, double-blind trial. *Am J Clin Nutr*. 1991;54:890-895.
7. West KP, Pokhrel RP, Katz J, et al. Efficacy of vitamin A in reducing preschool child mortality in Nepal. *Lancet*. 1991;338:67-71.
8. Herrera MG, Nestel P, El Amin A, Fawzi WW, Muhammad KA, Weld L. Vitamin A supplementation and child survival. *Lancet*. 1992;340:267-271.
9. Rahmathullah L, Underwood BA, Thulasiraj RD, et al. Reduced mortality among children in southern India receiving a small weekly dose of vitamin A. *N Engl J Med*. 1990;323:929-935.
10. Sommer A, Tarwotjo I, Djunaedi E, et al. Impact of vitamin A supplementation on childhood mortality: a randomized controlled community trial. *Lancet*. 1986;1:1169-1173.
11. Vijayaraghavan K, Radhaiah G, Prakasam B, Rameshwar KV, Reddy V. Effect of a massive dose of vitamin A on morbidity and mortality in Indian children. *Lancet*. 1990;336:1342-1345.
12. Daulaire NM, Starbuck ES, Houston RM, Church MS, Stukel TA, Pandey MR. Childhood

- mortality after a high dose of vitamin A in a high risk population. *BMJ*. 1992;304:207-210.
13. Muhilal, Permeisih D, Idjradinata YR, Muherdiyantiningsih, Karyadi D. Vitamin A-fortified monosodium glutamate and health, growth, and survival of children: a controlled field trial. *Am J Clin Nutr*. 1988;48:1271-1276.
14. Kothari G. The effect of vitamin A prophylaxis on morbidity and mortality among children in urban slums in Bombay. *J Trop Pediatr*. 1991;37:141.
15. Chalmers TC, Smith H, Blackburn B, et al. A method for assessing the quality of a randomized control trial. *Controlled Clin Trials*. 1981;2:31-49.
16. Detsky AS, Naylor CD, O'Rourke K, McGeer AJ, L'Abbe KA. Incorporating variations in the quality of individual randomized trials into meta-analysis. *J Clin Epidemiol*. 1992;45:255-265.
17. Rothman KJ. *Modern Epidemiology*. Boston, Mass: Little Brown & Co Inc; 1986.
18. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clin Trials*. 1986;7:177-188.
19. Coutsooudis A, Coovadia H, Broughton M, Salisbury R, Elson I. Micronutrient utilisation during measles treated with vitamin A or placebo. *Int J Vitam Nutr Res*. 1991;61:199-204.
20. United Nations Children's Fund. *The State of the World's Children, 1991*. Oxford, England: Oxford University Press; 1991.
21. World Health Organization. Joint WHO/UNICEF statement on vitamin A for measles. *Wkly Epidemiol Rec*. 1987;62:133-134.
22. Frieden TR, Sowell AL, Henning KJ, Huff DL, Gunn RA. Vitamin A levels and severity of measles: New York City. *AJDC*. 1992;146:182-186.
23. Arrieta A, Zaleska M, Stutman H, Marks M. Vitamin A levels in children with measles in Long Beach, California. *J Pediatr*. 1992;121:75-78.
24. Mejia LA. Vitamin A-nutrient interrelation-

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- ships. In: Bauernfeind JC, ed. *Vitamin A Deficiency and Its Control*. Orlando, Fla: Academic Press Inc; 1986.
25. Sivakumar B, Reddy V. Absorption of labelled vitamin A in children during infection. *Br J Nutr*. 1972;27:297-304.
26. Mahalanabis D, Simpson TN, Chakraborty ML, Ganguli C, Bhattacharjee AK, Mukherjee KL. Malabsorption of water miscible vitamin A in children with giardiasis and ascariasis. *Am J Clin Nutr*. 1979;32:313-318.
27. Wolbach S, Howe P. Epithelial repair in recovery from vitamin A deficiency. *J Exp Med*. 1933;57:511-526.
28. Nauss KM. Influence of vitamin A status on the immune system. In: Bauernfeind JC, ed. *Vitamin A Deficiency and Its Control*. Orlando, Fla: Academic Press Inc; 1986.
29. Abdeljaber MH, Monto AS, Tilden RL, Schork MA, Tarwotjo I. The impact of vitamin A supplementation on morbidity: a randomized community intervention trial. *Am J Public Health*. 1991;81:1654-1656.
30. Rahmathullah L, Underwood BA, Thulasiraj RD, Milton RC. 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*. 1991;54:568-577.
31. Arthur P, Kirkwood B, Ross D, et al. Impact of vitamin A supplementation on childhood morbidity in northern Ghana. *Lancet*. 1992;339:361-362.
32. Arroyave G, Bauernfeind J, Olson J, Underwood B. Selection of intervention strategies: IVACG Task Force on Intervention. In: *Guidelines for the Eradication of Vitamin A Deficiency and Xerophthalmia: A Report of the International Vitamin A Consultative Group (IVACG)*. New York, NY: The Nutrition Foundation Inc; 1977.