

Vitamin A supplementation and severity of pneumonia in children admitted to the hospital in Dar es Salaam, Tanzania¹⁻³

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See corresponding editorial on page 8.

ABSTRACT Vitamin A deficiency and acute lower respiratory tract infections coexist as important public health problems in many developing countries. We carried out a randomized, double-blind, placebo-controlled trial to examine whether large doses of vitamin A given to Tanzanian children who are admitted to the hospital with nonmeasles pneumonia would reduce the severity of respiratory disease. Six hundred eighty-seven children were randomly assigned to receive either placebo or vitamin A [200 000 IU (60 mg retinol equivalents) for children > 1 y of age and 100 000 IU (30 mg retinol equivalents) for infants] on the day of admission and another dose on the following day. Of the 346 children in the vitamin A group, 13 died in the hospital, compared with 8 of 341 children in the placebo group; the relative mortality was 1.63 (95% CI: 0.67, 3.97; $P = 0.28$). The mean number of days of hospitalization was the same in both groups (4.2 d). There were no differences between the vitamin A and placebo groups in the duration of hospital stay when examined within categories of children stratified by age, sex, breast-feeding status, nutritional status at baseline, or quartile of dietary vitamin A intake in the 4 mo before admission to the hospital. There were also no differences in the mean number of days of fever, rapid respiratory rate, or hypoxia, whether these endpoints were examined in the total number of subjects or in a subset with more severe clinical conditions at baseline. Large doses of vitamin A had no protective effect on the course of pneumonia in hospitalized Tanzanian children. *Am J Clin Nutr* 1998;68:187–92.

KEY WORDS Vitamin A, supplements, pneumonia, Tanzania, developing countries, children, respiratory tract infection

INTRODUCTION

Vitamin A deficiency and acute lower respiratory tract infections (ALRIs) coexist as important public health problems in many developing countries. About 190 million preschool children live in areas where they are at risk of vitamin A deficiency (1), whereas 4 million children die each year because of ALRIs and many more suffer from nonfatal respiratory infections (2). Vitamin A deficiency is associated with impaired humoral and cellular immune function, keratinization of the respiratory

epithelium, and decreased mucus secretion, which weaken barriers to infection (3). Vitamin A supplementation reduces the severity of respiratory infection and other systemic complications of measles (4). However, the relation between vitamin A status and nonmeasles ALRI is controversial. Vitamin A supplements reduced the risk of total mortality and diarrhea-specific mortality among children < 5 y of age who participated in several community-based trials. In the same studies, however, the supplements had no effect on the risk of pneumonia-related mortality (5). Vitamin A supplementation had no effect on the course of infection among Guatemalan children admitted to the hospital with pneumonia (6), whereas the supplements were associated with increased severity of disease in another trial in Peru (7).

We carried out a randomized, double-blind, placebo-controlled trial to examine whether large doses of vitamin A given to Tanzanian children who were admitted to the hospital with pneumonia reduced the severity of disease. The children were followed after discharge from the hospital to examine the effect of the supplements on the incidence and severity of subsequent infections and on survival. We report here the results of the hospital phase of the study.

SUBJECTS AND METHODS

The Tanzania Vitamin A Study was conducted between April 1993 and March 1997 in children between 6 and 60 mo of age who were admitted with pneumonia to Muhimbili Medical Center in Dar

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es Salaam. Pneumonia was diagnosed by a pediatric specialist on the basis of the presence of cough and one or more of the following signs: respiratory rate ≥ 40 breaths (50 breaths for infants between the ages of 6 and 11 mo) per minute, chest retractions, inability to eat or drink, the presence of decreased air entry, crackling sounds, or dullness to percussion. In most cases it was not possible to have a chest radiograph taken on the day of admission. Children who had received vitamin A supplements in the preceding 4 mo or had one or more of the following conditions were excluded from the study: weight-for-age $< 60\%$ of the World Health Organization median (8), measles, pulmonary tuberculosis, diphtheria, whooping cough, or xerophthalmia. The protocol was approved by the Human Subjects Committee of the Harvard School of Public Health, the Research and Publications Committee of Muhimbili University College of Health Sciences, and the Research and Ethics Committee of Tanzania Food and Nutrition Center. Informed consent was granted verbally by the mother or primary caretaker of the child. In total, 687 children were enrolled in the study.

Inquiries were made at baseline concerning background characteristics of the children, including feeding practices, immunizations, and sociodemographic variables such as the education of the parents, the number of siblings, and water and sanitary conditions in the household. Length (for children < 2 y of age) or height and weight were measured on the first day of admission to the hospital by using standard techniques. The subjects' dietary vitamin A intakes were assessed by administering to mothers a food-frequency questionnaire that was developed for use in this setting (9). The questionnaire included 64 food items; for each food, mothers were asked questions to ascertain the frequency of consumption in the 4 mo before hospitalization as well as the average portion size. Eligible children were randomly assigned in blocks of 20 to receive a dose of vitamin A or placebo on the day of admission and another dose on the following day. Vitamin A and placebo were dispensed with a dropper from identical 25-mL opaque bottles that were labeled with 1 of 4 batch numbers. Bottles with 2 of the 4 numbers contained corn oil (placebo), whereas bottles with the other 2 numbers contained vitamin A in corn oil at a concentration of 200 000 IU [60 mg retinol equivalents (RE)]/mL. Both placebo and vitamin A solutions contained a small amount of vitamin E (0.24 g/L) as an antioxidant to enhance the stability of the product over time. Children > 1 y received 1 mL solution on each of 2 d whereas infants were given half that amount. A single research supervisor was responsible for administering all treatments. The treatment regimens were prepared especially for the study by the Massachusetts College of Pharmacy and Allied Sciences, Boston, using raw material donated by Astra Pharmaceuticals, Westboro, MA. The batch number code was retained by the manufacturer until the end of the study. The vitamin A solution was examined with HPLC after 2 y of field storage and 95% potency was found.

One or 2 trained, full-time research nurses were available in the wards around the clock to administer research procedures and to assist a research pediatrician. Nonstudy nurses and physicians attended to the clinical needs of patients who received antibiotics and supportive therapy as practiced at Muhimbili Medical Centre. The study nurses measured the subjects' axillary temperatures with digital thermometers and measured respiratory rate and pulse with a stopwatch every 6 h. Fever was defined as temperature $> 37.8^\circ\text{C}$ whereas rapid respiratory rate was defined as ≥ 50 breaths/min for infants and ≥ 40 breaths/min for children > 1 y of age. The study pediatrician carried out a com-

TABLE 1

Sociodemographic and baseline clinical characteristics of children in the vitamin A and placebo groups¹

Characteristic	Vitamin A (n = 346)	Placebo (n = 341)
Child's age (%)		
6–11 mo	39.6	44.0
12–23 mo	36.7	31.7
24–35 mo	11.3	12.0
36–37 mo	9.3	8.8
≥ 48 mo	3.2	3.5
Boys (%)	53.6	54.9
Mean mother's age (y)	25.6 $\pm$ 5.2 ²	26.2 $\pm$ 5.4
Mother's education ³ (%)		
Low	15.6	16.8
Elementary	79.2	75.6
Secondary or postsecondary	5.2	7.7
Father's education ³ (%)		
Low	4.6	4.4
Elementary	75.4	73.2
Secondary or postsecondary	19.9	22.4
Number of persons in child's room (%)		
1–2	17.1	16.8
3	48.6	46.5
4	23.4	27.7
≥ 5	11.0	9.1
Household possessions (%)		
Bike	13.9	11.8
Car	2.6	3.2
Fan	29.5	28.8
Refrigerator	9.5	13.8
Radio	86.4	82.9
Full polio immunization, 4 doses (%)	94.4	94.0
Measles immunization (%)	51.7	52.9
Currently breast-fed (%)	68.8	66.2
Nutritional status ⁴ (%)		
Stunted	26.6	21.7
Wasted	13.6	13.8
Wasted and stunted	2.3	2.9
Normal	49.4	51.3
Unknown	8.1	10.3
Mean hemoglobin (g/L)	85.7 $\pm$ 23.7	85.0 $\pm$ 21.6
Mean erythrocyte sedimentation rate (mm/h)	48.6 $\pm$ 41.1	41.4 $\pm$ 35.2
Clinical signs at admission (%)		
Rapid respiratory rate (> 40 breaths/min)	99.7	99.7
Fever ($> 37.8^\circ\text{C}$)	34.3	37.9
PO_2 ($< 95\%$)	71.1	66.6
Dull percussion (%)	79.9	79.6
Decreased breath sounds (%)	92.8	93.3
Presence of crackling sounds (%)	97.7	97.1

¹ Percentages may not add up to 100.0 because of rounding.

² $\bar{x} \pm \text{SD}$.

³ Low education includes subjects with no education and those who attended Koranic school or adult education classes.

⁴ Wasted children were below -2 z scores in weight-for-height but at or above -2 z scores in height-for-age, stunted children were below -2 z scores in height-for-age but at or above -2 z scores in weight-for-height (8).

plete medical examination of all enrolled children and measured the oxygen saturation of the blood by using pulse oximetry (Novamatrix Medical Systems, Inc, Wallingford, CT) every day the children were in the hospital. Hypoxia was defined as $\text{PO}_2 < 95\%$. On the day of admission a total and differential white

TABLE 2

Clinical outcomes during hospitalization in the vitamin A and placebo groups

Outcomes	Vitamin A	Placebo	Relative risk (95% CI) ¹	P ²
Categorical outcomes				
Deaths in hospital	13 (3.8) ³	8 (2.4)	1.63 (0.67, 3.97)	—
Deaths or hospital stay >4 d	96 (27.8)	95 (27.9)	0.99 (0.71, 1.39)	—
Deaths or hospital stay >5 d	68 (19.7)	68 (19.9)	0.98 (0.68, 1.43)	—
Continuous outcomes				
Total population (n = 687)				
Length of hospital stay (d)	4.2 ± 3.7 ⁴	4.1 ± 3.4	—	0.79
Time with rapid respiratory rate, >40 breaths/min (d)	3.5 ± 3.3	3.3 ± 2.4	—	0.52
Time with fever, >37.8°C (d)	1.1 ± 2.3	1.1 ± 1.7	—	0.23
Time with hypoxia, PO ₂ <95% (d)	1.4 ± 2.1	1.3 ± 1.7	—	0.69
Subset with severe condition at baseline (n = 296) ⁵				
Length of hospital stay (d)	5.2 ± 4.9	4.4 ± 3.1	—	0.28
Time with rapid respiratory rate, >40 breaths/min (d)	4.6 ± 4.5	3.9 ± 2.6	—	0.49
Time with fever, >37.8°C (d)	1.9 ± 2.9	1.5 ± 1.6	—	0.51
Time with hypoxia, PO ₂ <95% (d)	2.0 ± 2.8	1.8 ± 2.0	—	0.92

¹Relative risks and CIs are from univariate logistic regression models.²Wilcoxon rank sum tests.³n; percentage in parentheses.⁴ $\bar{x} \pm$ SD.⁵Included children who had a respiratory rate >60 breaths/min, temperature >38.9°C, or PO₂ <90%.

blood count and hematocrit were obtained. The attending physician decided when to discharge each patient: when his or her respiratory rate was <40 breaths/min, temperature was ≤37.8°C, and the patient was able to eat and drink. For children who died in the hospital, the events that led to their deaths were recorded by the attending and research physicians and nurses.

Completed questionnaires were checked by the supervisors before double data entry and verification was done with dBaseIV (Ashton-Tate Corp, London). The Centers for Disease Control and Prevention Anthropometric Software Package (CASP; CDC, Atlanta) was used to calculate anthropometric indicators. All children with z scores below −2 were considered malnourished (10); such children were considered wasted if only deficient in weight-for-height, stunted if only deficient in height-for-age, or both stunted and wasted if they were deficient in both measures. Children at or above −2 z scores in both weight-for-height and height-for-age were classified as normally nourished. Vitamin A intake was computed by multiplying the frequency of consumption of each food by the nutrient content of the specified portions; the International Minilist nutrient database (11) and the East African food-composition tables (12) were used. The distributions of baseline characteristics between children in both groups were compared. The effect of the supplements was examined by comparing the mean of the following variables between the 2 groups: respiratory rate, temperature, and oxygen saturation during hospital stay; number of days of hospital stay; rapid respiratory rate; fever; and hypoxia. We examined the effect of the supplements in the total study population and within groups of children categorized by age (<12 mo, 12–23 mo, and ≥24 mo), sex, breast-feeding status, nutritional status, quartile of dietary vitamin A intake, and severity of clinical condition at baseline (defined as temperature >38.9°C, respiratory rate >60 breaths/min, or PO₂ <90%). Cox proportional hazards models were used to examine the effect of the supplements on the time to discharge from the hospital. Indicators of having an adverse event, defined as death or a hospital stay ≥5 d, were examined by using logistic regression.

Variances generated from these models were used to calculate 95% CIs. Data analysis was done by using the Statistical Analysis System (SAS; SAS Institute Inc, Cary, NC).

RESULTS

Six hundred eighty-seven children with pneumonia were eligible for enrollment in the trial. The distribution of sociodemographic and baseline clinical characteristics of the subjects were similar between children who received vitamin A and those who were given placebo (**Table 1**). Approximately 40% of the subjects were infants. Of the total number of children, ≈40% were undernourished, 25% were stunted, ≈13% were wasted, and 3% were both stunted and wasted. Most children were fully immunized against poliomyelitis.

Of the 346 children in the vitamin A group, 13 died in the hospital in contrast with 8 deaths in the 341 children in the placebo group; the relative mortality was 1.63 (95% CI: 0.67, 3.97; *P* = 0.28) (**Table 2**). There was no difference in the risk of prolonged hospital stay between children in the 2 experimental groups. The mean number of days in the hospital was the same in both groups (4.2 d). There were also no differences in the mean number of days of fever, rapid respiratory rate, or hypoxia, whether these endpoints were examined in the total number of subjects or among a subset with more severe clinical conditions at baseline, defined as children who had a respiratory rate >60 breaths/min, temperature >38.9°C, or PO₂ <90%.

Differences in mean temperature, respiratory rate, and PO₂ between children who received vitamin A and those who received placebo were examined between the second and fourth day in the hospital, ie, within 3 d of receiving the experimental treatment. There was a small difference on the third day of the hospital stay in mean respiratory rate: children in the vitamin A group took 49.2 breaths/min compared with 51.8 breaths/min in the placebo group (*P* = 0.02). No other significant differences were found.

There were no effects of vitamin A on the duration of hospi-

TABLE 3

Effect of vitamin A supplementation on duration of hospital stay in the total study population and for different values of various variables¹

Variable	Age- and sex-adjusted relative hazard (95% CI)	P
Overall effect of vitamin A supplements (<i>n</i> = 683)	0.96 (0.82,1.12)	0.58
Child's age		
6–11 mo (<i>n</i> = 283)	0.93 (0.73,1.18)	0.54
12–23 mo (<i>n</i> = 235)	0.98 (0.75,1.27)	0.86
≥24 mo (<i>n</i> = 165)	1.01 (0.74,1.37)	0.97
Sex		
Boys (<i>n</i> = 371)	0.89 (0.73,1.10)	0.29
Girls (<i>n</i> = 312)	1.05 (0.84,1.31)	0.70
Severe condition at baseline ²		
No (<i>n</i> = 373)	1.00 (0.81,1.23)	0.99
Yes (<i>n</i> = 265)	0.85 (0.66,1.09)	0.20
Breast-fed at baseline		
No (<i>n</i> = 222)	0.92 (0.70,1.21)	0.56
Yes (<i>n</i> = 460)	1.00 (0.83,1.20)	0.96
Nutritional status at baseline		
Stunted (<i>n</i> = 166)	1.17 (0.85,1.60)	0.34
Wasted (<i>n</i> = 94)	1.14 (0.75,1.72)	0.54
Wasted and stunted (<i>n</i> = 18)	0.44 (0.13,1.47)	0.18
Normal (<i>n</i> = 346)	0.83 (0.67,1.03)	0.09
Unknown (<i>n</i> = 59)	1.00 (0.58,1.72)	1.00
Dietary vitamin A intake		
Quartile 1 (lowest) (<i>n</i> = 138)	0.91 (0.65,1.29)	0.61
Quartile 2 (<i>n</i> = 160)	1.00 (0.72,1.40)	0.98
Quartile 3 (<i>n</i> = 154)	0.88 (0.64,1.22)	0.45
Quartile 4 (highest) (<i>n</i> = 154)	1.10 (0.80,1.52)	0.54

¹ From individual Cox proportional hazards models; outcome variable was time to discharge from hospital. Relative risk values >1 indicate a beneficial effect, ie, the factor was associated with shorter stay in the hospital whereas values <1 indicate a harmful effect, ie, the factor was associated with a longer stay.

² Children with a severe condition at baseline had a respiratory rate > 60 breaths/min, temperature > 38.9°C, or PO_2 < 90%.

tal stay when examined within categories of children stratified by age, sex, breast-feeding status, or nutritional status at baseline. The effects of vitamin A were also similar within quartiles of dietary vitamin A intake in the 4 mo before admission to the hospital (Table 3). To examine the effect of the supplements in children in more extreme categories of intake, we grouped children by deciles of dietary vitamin A intake. Vitamin A supplements had no effect on the duration of hospitalization of children in the lowest or highest decile of prior vitamin A intake.

Dietary intake of vitamin A was not independently associated with having an adverse event, defined as death or a hospital stay ≥ 5 d (Table 4). As expected, baseline temperature, respiratory rate, and PO_2 were significant predictors of patients experiencing an adverse event. Compared with children whose respiratory rate was < 50 breaths/min, those who had a respiratory rate > 60 breaths/min were twice as likely to die or stay in the hospital for a longer period.

DISCUSSION

Vitamin A supplementation had no effect on the clinical course of disease in Tanzanian children admitted to the hospital with pneumonia. The extent of vitamin A deficiency in a particular population is likely to be an important factor in determining

TABLE 4

Factors associated with an adverse outcome during the hospital stay, defined as death or a hospital stay ≥ 5 d¹

Variable	Relative risk (95% CI)	P for trend ²
Supplement		
Vitamin A (<i>n</i> = 335)	0.95 (0.65,1.41)	0.81
Placebo (<i>n</i> = 322)	1.0	
Dietary vitamin A intake		
Quartile 1 (lowest) (<i>n</i> = 136)	1.0	0.81
Quartile 2 (<i>n</i> = 156)	1.55 (0.84,2.84)	
Quartile 3 (<i>n</i> = 150)	1.66 (0.90,3.06)	
Quartile 4 (highest) (<i>n</i> = 144)	1.03 (0.53,2.03)	
Temperature at admission		
< 37.2°C (<i>n</i> = 147)	1.0	0.0001
37.2–37.5°C (<i>n</i> = 158)	1.67 (0.76,3.65)	
37.6–38.3°C (<i>n</i> = 218)	3.43 (1.71,6.89)	
> 38.3°C (<i>n</i> = 130)	7.44 (3.63,15.23)	
Respiratory rate at admission		
< 50 (breaths/min) (<i>n</i> = 240)	1.0	0.0001
51–60 (breaths/min) (<i>n</i> = 206)	0.94 (0.55,1.58)	
> 60 (breaths/min) (<i>n</i> = 207)	2.08 (1.30,3.33)	
Oxygen saturation at admission		
95–100% (<i>n</i> = 173)	1.0	0.02
90–94% (<i>n</i> = 333)	0.60 (0.37,0.97)	
< 90% (<i>n</i> = 56)	2.08 (1.07,4.06)	
Hemoglobin		
> 100 g/L (<i>n</i> = 167)	1.0	0.001
85–99 g/L (<i>n</i> = 150)	2.49 (1.29,4.79)	
70–84 g/L (<i>n</i> = 131)	2.12 (1.07,4.22)	
< 70 g/L (<i>n</i> = 141)	3.94 (2.08,7.47)	
Erythrocyte sedimentation rate		
< 16 mm/h (<i>n</i> = 143)	1.0	0.02
16–30 mm/h (<i>n</i> = 120)	1.52 (0.80,2.92)	
31–60 mm/h (<i>n</i> = 120)	1.80 (0.95,3.42)	
> 60 mm/h (<i>n</i> = 139)	2.01 (1.08,3.73)	

¹ From individual logistic regression models that included age of child, sex, mother's education, number of possessions in the household, and number of persons per room in the household, in addition to dummy variables of the risk factor of interest.

² Obtained by including each risk factor as a continuous variable in a logistic regression model with the same covariates.

the degree of efficacy of large doses of vitamin A; the supplements are likely to be more efficacious in children who are deficient than in those who are not. We did not measure serum retinol concentrations in this population because they would have been low as a result of the infection, even in the absence of actually deficient liver stores (13). Instead, we assessed dietary vitamin A intake in children in the 4 mo before enrollment and used it as a proxy for vitamin A status at random assignment. The median intake was found to be 420 µg RE/d. Given that the recommended dietary allowance for children < 5 y of age is ≈ 400 µg RE/d for children 1–3-y old and 500 µg RE/d for children 4–6-y old (14), this finding suggests that vitamin A deficiency is not a serious problem in this study population and provides a possible explanation for the lack of effect of the supplements. However, the supplements had no effect even in children in the lowest decile of dietary intake, whose median intake was 152 µg RE/d. We are in the process of validating a food-frequency questionnaire for use in this population. Although vitamin A deficiency does not appear to be a major problem in this study population on the basis of dietary intake, green leafy vegetables (which are the main source of dietary vit-

amin A in this case) may have a limited effect on vitamin A status because of limited bioavailability (15). Vitamin A deficiency is likely to be more prevalent among malnourished children, who were excluded from the study for ethical reasons.

Our findings of no effect of vitamin A supplements agree with the results of another trial that was carried in children with pneumonia in Guatemala (6), are but different from those of supplementation trials carried out in measles patients. In Tanzania (16) and South Africa (17, 18), vitamin A supplementation resulted in significant reductions in the risk of mortality and gastrointestinal and respiratory complications of measles. These different effects of vitamin A supplements may be explained by differences in the pathogenesis and immune response of measles and pneumonia. After gaining entry to the host via the upper respiratory tract, the measles virus replicates in the reticuloendothelial system and a few days later viremia spreads to the skin and gastrointestinal and respiratory epithelia (19). By enhancing both humoral and cellular immunity, vitamin A supplementation in cases of measles may reduce the negative effect of the viremia on the respiratory and other systems. On the other hand, pneumonia is limited to the respiratory system in most uncomplicated cases, which were the majority of cases in both the Tanzanian and Guatemalan pneumonia trials. Immune function, particularly phagocytosis and activated complement, are crucial for the prevention of pneumonia (20, 21). The effect of vitamin A on these nonspecific immune variables is controversial, possibly because the studies examining this question were different in design, species, doses of vitamin A, and background vitamin A deficiency. The effect of retinol supplements on phagocytosis and killing ability of polymorphonuclear leukocytes and macrophages varied from being inhibitory (22), to showing no effect (23, 24), to causing enhanced function (25).

In vitamin A-deficient subjects, there is extensive desquamation of the respiratory epithelium (26) and greater adherence of bacteria to the damaged epithelium (27). Adequate vitamin A status is likely to promote the healing of the damaged epithelial lining, thereby reducing the incidence or severity of pneumonia. However, provision of vitamin A supplements during the episode of infection may not provide adequate time for this healing process to occur.

Although the role of vitamin A in reducing the severity of localized respiratory infection may be limited, by enhancing specific antibody production (28), vitamin A supplementation may be protective in cases of pneumonia that are more severe than those seen in the Tanzanian and Guatemalan trials. Protective effects may be seen in cases of invasive, bacteremia-associated pneumonia, similar to the role of vitamin A in viremia-induced complications in measles. Although vitamin A supplements were without an effect on the course of pneumonia in the total study population in a recent trial in Brazil (29), there was an apparent protective effect among a subgroup of children who had pneumonia severe enough to warrant hospitalization. However, all subjects enrolled in the Tanzanian trial were hospitalized and we observed no effect of the supplements among a subset of children who had a more severe condition at baseline. Also, in community-based vitamin A trials the supplements were essentially without effect on mortality, presumably because of severe and invasive respiratory infection (4, 5). It is worth noting, however, that cause-specific mortality was ascertained in these trials by using verbal autopsy tools that have not been validated.

It is possible that large doses of vitamin A may be harmful

when given to children who are well-nourished or specifically vitamin A sufficient, as hypothesized by investigators in 2 studies from Indonesia and Nepal. In Indonesia (30), large doses of vitamin A tended to be protective in chronically malnourished children but resulted in a significant increase in risk of pneumonia in children with adequate nutritional status. In Nepal (31), better-nourished infants < 6 mo of age experienced an apparent increase in mortality as a result of vitamin A supplementation. We observed a 60% increase in mortality among apparently vitamin A-sufficient children enrolled in the Tanzanian trial, although this finding was not statistically significant. However, with the sample size of the study, the statistical power to examine the effect of the supplements on this endpoint was limited. In a placebo-controlled trial in Peru (7), children with pneumonia who received vitamin A supplements had lower blood oxygen saturation and had greater need for supplemental oxygen, although there was no difference in the duration of hospital stay between the 2 groups. This Peruvian study had a small sample size ($n = 95$) and children with a wide age range were enrolled (3 mo to 10 y). However, the apparently harmful effect of vitamin A supplements in the studies from Indonesia (30) and Nepal (31), and the apparent increase in mortality in supplemented children in our Tanzanian trial, suggest that more research is needed to understand the conditions under which vitamin A supplements may result in adverse effects. Unfortunately, baseline vitamin A status was not measured in most of the large mortality trials so that the possibly different effect of the supplements could be examined in children stratified by vitamin A status.

The World Health Organization proposed a disease-targeted distribution of large doses of vitamin A to children who present to health care facilities with pneumonia, diarrhea, or malnutrition (32). Although vitamin A supplements did not reduce the severity of pneumonia in this study, supplements will replenish vitamin A stores that may have been depleted as a result of infection. In pneumonia and other infections, increased use of vitamin A stores expose the child to a higher risk of vitamin A deficiency and associated higher risk of diarrhea-specific mortality (4). Excretion of vitamin A in the urine has also been reported during pneumonia episodes, which, if it continues for several days could significantly reduce liver stores of vitamin A (33). In countries where vitamin A deficiency is a serious public health problem, the disease-targeted distribution system of vitamin A supplements is a more efficient approach to delivering the supplements than is periodic dosing of all children in a community; however, a system to prevent administering multiple, large doses to children in a short period of time needs to be put in place. In addition, in light of a possible harmful effect of vitamin A supplements in a certain subset of children hospitalized with pneumonia, as suggested by the recent study from Peru (7) and the increased mortality of supplemented children in this study, vitamin A supplements should be given at the time of discharge from the hospital rather than at admission. In countries where vitamin A-containing foods are abundant, however, programs to increase the consumption of these foods need to be designed, because this approach is likely to be safer and more sustainable than supplementation programs. 

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