Effects of moderate doses of vitamin A as an adjunct to the treatment of pneumonia in underweight and normal-weight children: a randomized, double-blind, placebo-controlled trial[1–4]

Alicia Rodríguez, Davidson H Hamer, José Rivera, Mario Acosta, Gilda Salgado, Martha Gordillo, Myryam Cabezas, Carlos Naranjo-Pinto, Julio Leguísamo, Dinor Gómez, Guillermo Fuenmayor, Edgar Játiva, Gladys Guamán, Bertha Estrella, and Fernando Sempértegui

ABSTRACT

Background: Randomized controlled trials have shown inconsistent responses of childhood pneumonia to the use of vitamin A as an adjunct to the standard treatment of pneumonia.

Objective: We evaluated the effect of a moderate dose of vitamin A as an adjunct to standard antimicrobial treatment on the duration of respiratory signs in children with pneumonia.

Design: Children, aged 2–59 mo, with pneumonia and weight-for-age <50th percentile who had been admitted to the Baca Ortíz Children's Hospital in Quito, Ecuador, were randomly assigned to receive 50 000 IU (aged 2–12 mo) or 100 000 IU (aged >12–59 mo) vitamin A or a placebo.

Results: Of the 287 children enrolled, 145 received vitamin A and 142 received placebo. No overall differences were observed between the 2 groups in the duration of signs of pneumonia. Multiple linear regression showed a significant interaction between basal serum retinol concentration and vitamin A group for the time (in h) to remission of respiratory signs ($\beta = -3.57$, SE = 1.09, $P = 0.001$). Duration of clinical signs was less in children with basal serum retinol concentrations >200 μg/L who received vitamin A supplements than in children with similar concentrations who received placebo (69.9 ± 49.9 h compared with 131.3 ± 143.9 h; $P = 0.049$).

Conclusions: Overall, we found no effect of a moderate dose of vitamin A supplementation on the duration of uncomplicated pneumonia in underweight or normal-weight children aged <5 y. However, a beneficial effect was seen in children with high basal serum retinol concentrations. *Am J Clin Nutr* 2005;82:1090–6.

KEY WORDS Vitamin A, pneumonia, underweight, normal-weight, children, duration of signs of pneumonia

INTRODUCTION

Acute respiratory infections (ARIs) account for ≈2.1 million deaths per year in children aged <5 y (1). In the Americas, ≈140 000 children aged <5 y die of pneumonia each year; children aged <1 y are most likely to be affected (2).

Acute lower respiratory infections (ALRIs) are a global problem, and there are large differences in mortality rates between developed and resource-poor countries (3–5). Pneumonia is responsible for only 1–3% of deaths of children aged <5 y in developed countries, but it is responsible for 10–25% of deaths of children aged <5 in resource-poor countries (6).

Observational studies have shown that children with vitamin A deficiency are at greater risk of illness and death due to infections of the respiratory tract than are vitamin A–replete children (7–10). Unique to pneumonia associated with measles, supplementation with megadoses of vitamin A (total of 400 000 IU within 24 h of the enrollment) has a clear protective effect (11, 12). In nonmeasles ALRIs, the results have been contradictory: some studies found a protective effect of megadoses (8–13), but others did not (14–16). Although most studies of ALRIs used supplements with large doses of vitamin A every 4 to 6 mo, a study that used small doses (10 000 IU) of vitamin A, given weekly, found that lower doses were associated with a low risk of respiratory tract infections in malnourished Ecuadorian children (17).

Large doses of vitamin A, when used as an adjunct to standard therapy, were associated with a significant shortening of hospitalization of children with pneumonia in one study (18). However, other studies did not show a beneficial effect of vitamin A on the duration of pneumonia signs or subsequent morbidity in children aged >6 mo (19–22). In contrast, a study conducted in Peru found that the recovery in children aged 3 mo to 10 y who

[1] From the Corporación Ecuatoriana de Biotecnología, Quito, Ecuador (AR, BE, and FS); the Instituto de Ciencia y Tecnología, Ministerio de Salud Pública, Quito, Ecuador (AR and GG); the Center for International Health and Development, Boston University School of Public Health, Boston, MA (DHH); the Tufts University Gerald J and Dorothy R Friedman School of Nutrition Science and Policy, Medford, MA (DHH); the Universidad Central del Ecuador, Escuela de Medicina, Quito, Ecuador (JR, BE, and FS); and the Hospital de Niños Baca Ortiz, Quito, Ecuador (MA, GS, MG, MC, CN-P, JL, DG, GF, and EJ).

[2] The opinions expressed herein are those of the authors and do not necessarily reflect the views of USAID. The funding agencies did not influence the conduct or outcomes of the analysis or exercise any editorial control over this paper.

[3] Supported by the United Nations International Children's Emergency Fund (UNICEF), the Thrasher Maternal and Child Health Foundation, and a Cooperative Agreement between Boston University and the Office of Health and Nutrition of the United States Agency for International Development (USAID).

[4] Address reprint requests to F Sempértegui, Corporación Ecuatoriana de Biotecnología, Ave. Colón N1468 y Nueve de Octubre, Of. 508, Quito, Ecuador. E-mail: fersempert@andinanet.net.

Received February 1, 2005.

Accepted for publication August 5, 2005.

were hospitalized with pneumonia and who received supplements of high doses of vitamin A (150 000 and 300 000 IU given in 2 doses) was adversely affected (23).

In hospitalized, malnourished children with vitamin A deficiency, high doses of vitamin A (100 000 and 200 000 IU) did not reduce morbidity. However, lower daily doses (5000 IU from the time of admission until discharge) were more beneficial in children with severe malnutrition in terms of reducing the subsequent risk of severe diarrhea but not of reducing ALRI or all-cause fevers (24).

Given the mixed results of therapeutic trials of vitamin A in children with pneumonia and the limited evidence that smaller doses may be protective in underweight children, we conducted a randomized, double-blind, placebo-controlled trial. The purpose of the current trial was to assess the effect of supplementation with moderate doses of vitamin A as an adjunct to standard treatment of pneumonia in normal-weight and underweight children aged 2–59 mo on the duration of hospitalization and clinical signs of pneumonia.

SUBJECTS AND METHODS

Study design

This was a randomized, double-blinded, placebo-controlled clinical trial of orally administered vitamin A in doses of 50 000 IU to children aged 2–12 mo and of 100 000 IU to children aged >12 to 59 mo who were admitted to the Baca Ortíz Children's Hospital in Quito, Ecuador. The enrollment period extended from May 2002 to June 2004. During this time, the treatment protocols in the hospital did not vary, and no important changes were observed in recruitment, enrollment, and follow-up.

Study site

Baca Ortiz is the main pediatric reference hospital in Ecuador. During 2001, 26 713 children were treated in the outpatient departments and emergency room. ARI is the most common cause of admission to the hospital. During 2001, of a total of 5599 admissions, 977 were children with pneumonia (Department of Statistics, Baca Ortiz Hospital, unpublished data, 2001).

Subjects

The average duration of hospitalization of children with pneumonia was 5.07 ± 2.87 d, according to a preliminary study in the Baca Ortiz Hospital. To detect a difference of 1 d of hospitalization with 80% power, with an α of 0.05, 2-tailed study, the required sample size was 141 children per group. The estimated dropout rate was 15%. Therefore, the number of children to be enrolled was 162 per group.

Children aged 2–59 mo who had a clinical diagnosis of pneumonia confirmed by X-ray and weight-for-age < 50th percentile, according to the US National Center Health of Statistics growth curve (25), were included. Clinical pneumonia was defined as the presence of an elevated respiratory rate (>40/min in children aged >12 to 59 mo; >50/min in children aged 2–12 mo), fever (axial temperature >37.5 °C), cough or chest indrawing or both, and low oxygen saturation (pulse oximetry level < 90%), and at least one clinical sign by auscultation (eg, rales, wheezing, diminished breath sounds, bronchial breath sounds, or pleural rub). Chest X-ray was considered positive if at least one of the following radiologic signs compatible with pneumonia was present: focal infiltrate, consolidation, or minimal pleural effusion. A pulmonary specialist read all chest X-rays to verify the findings.

The physicians of the study team were familiarized with all study procedures during a pilot phase to ensure standard practices during the study. Severely malnourished children and children with another acute infection, severe anemia (hemoglobin concentration <80 g/L), complicated pneumonia or pneumonia resulting from aspiration of a foreign body, congenital abnormalities, hospitalization for any reason during the previous 2 mo, or children who were given megadoses of vitamin A at a health center in the previous 2 mo were excluded.

Eligible children were randomly assigned to receive either vitamin A or placebo. Randomization was performed in blocks of 20. A randomization list was generated by using tables of random numbers and was converted into a sequence of envelopes that contained the regimen assignments for all children in the trial. Once an eligible child was identified, the next envelope in the sequence was opened, and the corresponding regimen was provided to the child. The Ethical Committee of the Corporación Ecuatoriana de Biotecnología held the blinded randomization codes in a secure place. The study code was not broken until all the data were entered and the initial analyses performed.

Written informed consent was obtained from the parent or care provider of each child for enrollment of the child in the study. The study protocol and informed consent form were approved by the Boston University Institutional Review Board and the Ethics Committee of the Corporación Ecuatoriana de Biotecnología, which also supervised the study to ensure that study procedures were being followed correctly. The Ethics Committee also served as the Data Safety Monitoring Board, conducted an interim review of safety data and a blinded interim analysis when data accrual was slightly more than half completed. From its review, the Data Safety Monitoring Board recommended the continuation of the study without any procedural changes.

Study definitions

Underweight was defined a weight-for-age z score ≤ -2 SD. Normal-weight was defined as weight-for-age z score > -2 SD.

Criteria for discharge included resolution for ≥12 h of all of the following: tachypnea (respiratory rate ≤ 40/min in children aged >12 to 59 mo or ≤50/min in children aged 2–12 mo), fever (axillary temperature ≤37.5 °C), and hypoxemia (oxygen saturation ≥90%).

Study procedures

A child enrolled in this study was randomly assigned to 1 of the 2 groups (vitamin A or placebo). Vitamin A and placebo capsules were manufactured by Tishcon Corporation (Westbury, NY). The capsules were kept in opaque plastic containers and stored in a dry, cool location.

A baseline blood test (3 mL) was performed by venipuncture on arrival (0 h) and again at 72 h for measurement of serum retinol. Respiratory frequency, axillary temperature, and pulse oximetry were monitored every 6 h by a physician, nurse, or trained medical student from the study staff. Other clinical signs and auscultation of the lungs were performed every 24 h by a study physician. A chest X-ray was performed on arrival (0 h) and at 72 h to assess the differential radiologic response between the 2 groups.

All children were given the standard antibiotic treatment for pneumonia used at the Baca Ortiz Hospital: ampicillin as initial therapy in children aged <2 y or penicillin in children aged ≥2 y. Gentamicin was added if the child's condition deteriorated within 24 h of admission. A third-generation cephalosporin with or without oxacillin was given if the child continued to deteriorate over the next few days. In a limited number of children whose clinical condition became critical, an antibiotic regimen that was different from the regimens described above was used, according to the physician's judgment. Additional therapeutic measures included the administration of oxygen, intravenous fluids if required, and salbutamol for wheezing.

For ethical reasons, at the time of medical discharge, all enrolled children were given a single dose of vitamin A. Children aged 2–12 mo were given 50 000 IU, and children aged >12–59 mo were given 100 000 IU.

Plasma retinol was measured by HPLC as described (19). Plasma samples were recoded so that the laboratory technicians were blinded to the basal and final samples. Hemoglobin was measured by using a portable unit (Hemocue, Angelholm, Sweden). Chest X-rays were done with a Genetron 650 machine (General Electric, Milwaukee, WI).

Statistical analysis

Data were collected by using questionnaires specific to the project, all of which were standardized and validated during a pilot phase conducted from April to June 2001. The supervisor examined the questionnaires weekly and resolved any inconsistencies with the physician responsible for the treatment of the child. Data entry and management were done with ACCESS 2000 premium software (version 9.0.69265P3; Microsoft, Redmond, WA). Statistical analyses were done with SPSS statistical software (version 11.5.0; SPSS Inc, Chicago, IL). Descriptive statistics were calculated for all baseline measurements (ie, age, sex, weight-for-age *z* score, height-for-age *z* score, hemoglobin and retinol concentrations, respiratory signs, and chest X-ray findings) and variables collected by questionnaire (breastfeeding), and they were compared between the vitamin A and placebo groups.

Total hours of remission of each sign (ie, tachypnea, fever, and hypoxemia) and remission of all 3 signs together as well as total days of diminished breath sounds, bronchial breath sounds, and pleural effusion were calculated and compared by treatment arm. The same statistics were examined by age, nutritional status, basal serum retinol concentration, and severity of hypoxemia (O_2 saturation <80%). The differences between means and proportions were analyzed by using *t* and chi-square tests, respectively. The level of significance accepted was ≤0.05. Differences in the time (h) to resolution of all 3 signs were compared by using the log-rank test for homogeneity for Kaplan-Meier survival curves (26).

A multiple linear regression model was developed to assess the effect of vitamin A on the time (h) to resolution of clinical signs of pneumonia while controlling for the predictor variables that were important as potential confounders of the analysis. Regression diagnostic was performed, and the adequacy of covariate functional forms was examined. The summary includes regression coefficient (β), SE, and the *P* value corresponding to 2-sided testing of 0 regression effects.

RESULTS

A total of 1319 children with probable pneumonia were screened, and 287 children were enrolled in the study (**Figure 1**). Chief causes of exclusion were weight > 50th percentile, oxygen saturation >90%, age <2 mo, and receipt of megadoses of vitamin A during the previous 2 mo. Of the children enrolled, 121 (41.1%) were girls and 152 (53%) were infants aged 2–12 mo. Eighty-three (29%) children were underweight. At enrollment, no significant differences were observed between the vitamin A and placebo groups in terms of age, sex, weight-for-age *z* score, hemoglobin concentration, plasma retinol concentration, oxygen saturation, respiratory signs, or chest X-ray findings (**Table 1**).

During the study, 5 deaths occurred, which were equally distributed in the 2 study arms. Forty-eight children (16.7%) were lost to follow-up during the course of the study. The main causes of dropping out were parental requests for discharge against medical advice and clinical findings of exclusion criteria identified shortly after enrollment (Figure 1).

The Kaplan-Meier survival curves for time to remission of all 3 signs are shown in **Figure 2**. No significant differences were observed between the vitamin A and placebo groups for the primary outcome—the time to remission of all 3 signs ($P = 0.35$). In addition, no significant difference was observed between the 2 groups in terms of the duration of each respiratory sign. Resolution of focal infiltrates at 72 h did not differ significantly between the 2 groups (**Table 2**).

The final plasma retinol concentration did not differ significantly between the groups at 72 h (vitamin A group: 273 ± 107 μg/L; placebo group: 285 ± 112 μg/L). The change from baseline to 72 h as did not differ significantly (vitamin A group: 120 ± 107 μg/L; placebo group: 122 ± 119 μg/L).

We did not find any significant difference in the duration of respiratory signs when the 2 groups were stratified by baseline nutritional status or by age (≤12 or >12 mo) (data not shown). Time to resolution of respiratory symptoms did not differ significantly between underweight and normal-weight children (97.3 ± 77.11 and 111.5 ± 84.4 h, respectively; $P = 0.25$), independent of the treatment arm.

No significant difference was observed in the primary outcome in the 2 groups for children with severe pneumonia as defined by the WHO (27). However, children with room air oxygen saturation <80% who were given placebo spent 25 h less time in the hospital than did children who were given vitamin A. However, this difference was not significant ($P = 0.1$).

A multiple regression analysis was performed to test predictors of time to clinical resolution of pneumonia. The model included the basal data of the following covariates: treatment arm and sex (dichotomous variables), age, weight-for-age *z* score, height-for-age *z* score, hemoglobin concentration, and serum retinol concentration (continuous variables) and interaction between treatment arm and basal serum retinol. In this model, the only significant finding was an interaction between basal serum retinol concentration and vitamin A group for the time to remission of respiratory signs (in h) ($\beta = -3.57$, SE = 1.09, $P = 0.001$). **(Figure 3)**.

When children were stratified according to basal serum retinol concentration (≤200 and >200 μg/L), the time to remission of all 3 respiratory signs was significantly lower in children with higher basal serum retinol concentrations in the vitamin A group ($n = 25$) than in their counterparts in the placebo group ($n = 27$)

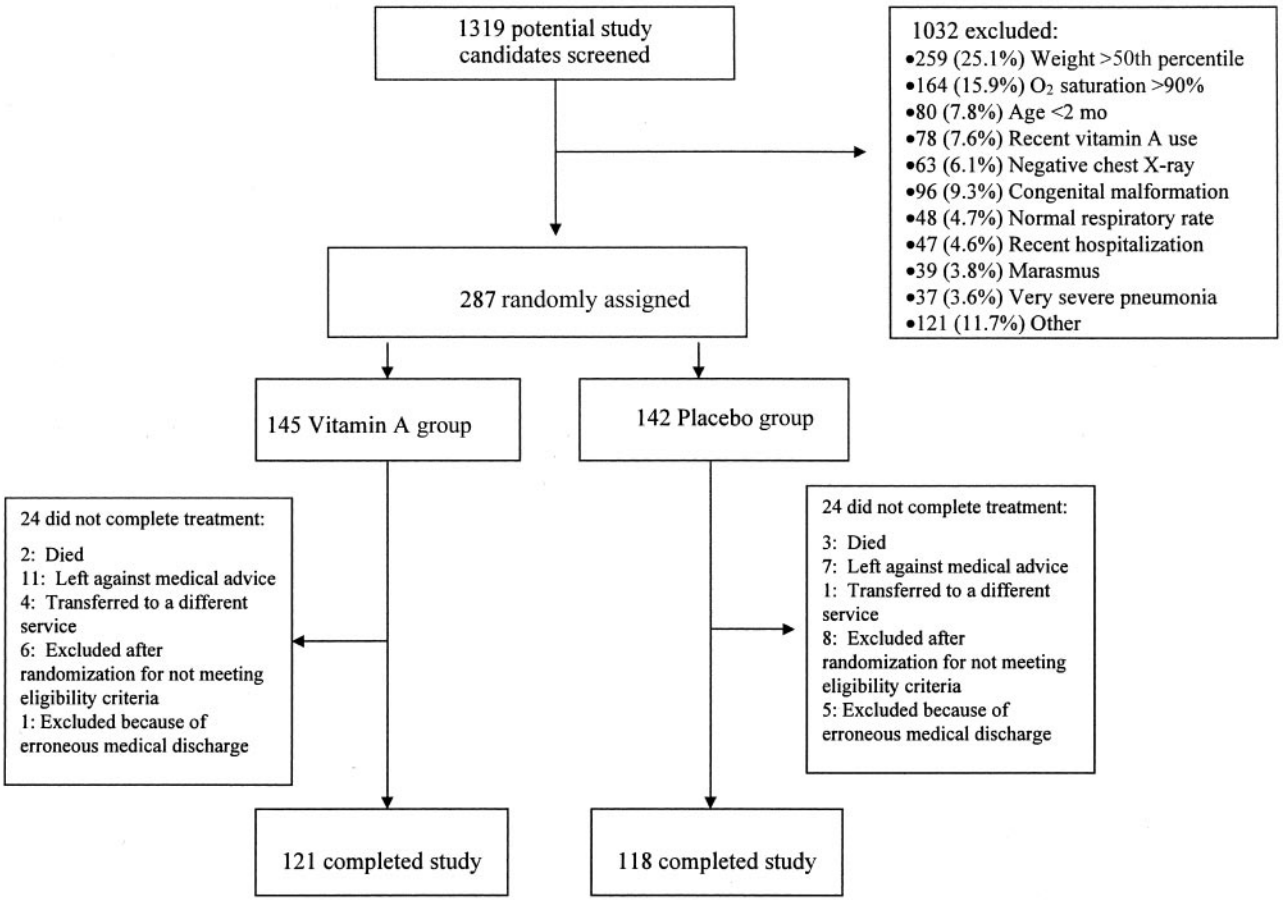

FIGURE 1. Study profile.

(vitamin A group: 69.9 ± 49.9 h; placebo group: 131.3 ± 143.9 h; $P = 0.049$). The Kaplan-Meier survival analysis for time to remission of all 3 respiratory signs showed a significant difference between vitamin A and placebo groups in children whose basal serum retinol was >200 μg/L ($P = 0.0116$).

DISCUSSION

Overall, we did not find any effect of supplementation with low-dose vitamin A on the time to clinical recovery in children aged between 2 and 59 mo with pneumonia. Although we used a smaller dose of vitamin A (50 000 and 100 000 IU) than did previous studies, our results are in agreement with those of studies in Tanzania (19), Guatemala (22), and the United States (28), all of which used megadoses of vitamin A.

In Vietnam, Si et al (29) reported a significant reduction in the duration of hospitalization for pneumonia in children with moderate malnutrition ($P = 0.04$). This finding was predominantly due to a beneficial effect of the vitamin A supplement in girls aged >1 y, so the significance of this result is controversial. As others have shown (24), we did not find an effect of supplementation in children with moderate undernutrition (either underweight or stunted). In contrast to our hypothesis, the time to remission of respiratory signs did not differ significantly between the groups of normal-weight children and those of underweight children, independent of the type of the intervention. Because severely underweight and wasted children were excluded from participation in our study, the potential utility of vitamin A as an adjunct to the treatment of pneumonia in this high-risk group remains unknown.

Previous community-based studies in Ecuador showed that the prevalence of vitamin A deficiency is relatively low (14%) (30–32). We found that ≈75% of children admitted to the hospital had subclinical vitamin A deficiency, as suggested by a plasma retinol concentration <200 μg/L. This difference most likely was a result of the acute inflammatory response resulting from the episode of pneumonia, which resulted in a decrease in serum retinol in a large proportion of our study participants. Several mechanisms are possible by which serum retinol concentrations decrease during the acute phase response to infection. First, there are low synthesis and release of retinol-binding protein, the main transport protein for retinol, from the liver during acute inflammation in experimental models (33–35). Second, there may be greater exogenous losses (36, 37) or metabolic needs (38) or both. One community-based study conducted in a population of poor children in Ecuador evaluated retinol stores by using the modified relative dose response test and found that 26% of children had low stores. Those children had had fever and respiratory or diarrheal infections in the previous 3 wk (39). Therefore, the low baseline concentrations of serum retinol we found in the current study probably were transiently depressed as a result of the acute phase response. In support of this hypothesis,

TABLE 1
Baseline characteristics of subjects[1]

	Vitamin A group (n = 145)	Placebo group (n = 142)
Age (mo)	14.2 ± 10.4[2]	15.5 ± 13.2
2–12 mo [n (%)]	78 (53.8)	74 (52.1)
>12 mo [n (%)]	67 (46.2)	68 (47.9)
Female (%)	40	44
Weight-for-age z score	−1.56 ± 1.16	−1.27 ± 1.33[3]
<−2 [n (%)]	49 (33.8)	34 (23.9)
−2 to −1 [n (%)]	52 (35.9)	57 (40.1)
>−1 [n (%)]	44 (30.3)	50 (35.2)
Hemoglobin (g/L)[4]	112 ± 16.9	113 ± 14.8
Retinol (μg/L)[5]	152 ± 64.5	162 ± 70.2
Percentage of O_2 saturation	79.8 ± 8.87	79.8 ± 6.51
Breastfeeding (%)	68.8	64.1
Respiratory signs		
Respiratory rate	60.2 ± 10.6[6]	60.3 ± 10.3
2–12 mo	63 ± 9.63	61.9 ± 10.0
>12 mo	55.8 ± 10.0[7]	58.5 ± 10.4
Pleural rub (%)	1.4	1.4
Rales (%)	95.9	92.3
Bronchial breath sounds (%)	4.8	6.4
Diminished breath sounds (%)	63.4	57.7
Chest X-ray		
Infiltrates (%)	89.7	88.7
Consolidation (%)	27.6	31.0
Pleural effusion (%)	4.1	5.6

[1] Differences were not significant. Data for percentages were analyzed with the chi-square test.
[2] $\bar{x}$ ± SD (all such values). Data were analyzed with Student's t test.
[3] n = 141.
[4] n = 139 and 140 in the vitamin A and placebo groups, respectively.
[5] n = 137 and 134 in the vitamin A and placebo groups, respectively.
[6] n = 144.
[7] n = 66.

we found a substantial increase (≈125%) in retinol concentrations at 72 h in both groups. These results are in agreement with those of Nacul et al (40), who also found an increase of retinol concentrations in both supplemented and placebo groups. This increase may be due to the neoliberation of retinol from liver stores, once the production of retinol-binding protein is restored after the acute infection has resolved.

There were several limitations to our study. First, because of a shortage of funding and a length of time for enrollment that was greater than originally predicted, we were unable to reach the target sample size. However, enrollment was nearly 90% of the estimated necessary sample size, which was enough to detect differences at 80% power. Given the lack of difference in all primary outcomes between the 2 groups, the additional 10% of the estimated sample size probably would not have made a meaningful difference in these outcomes. Second, the proportion of children who were lost to follow-up was slightly higher than that estimated in our sample size estimation. However, this minimal difference also was unlikely to have had an important effect on the primary outcomes. Third, we did not measure any indicators of the acute phase response. Although this measurement would have been helpful in a better assessment of the baseline and change in serum retinol concentrations, it would not have contributed to the primary outcomes.

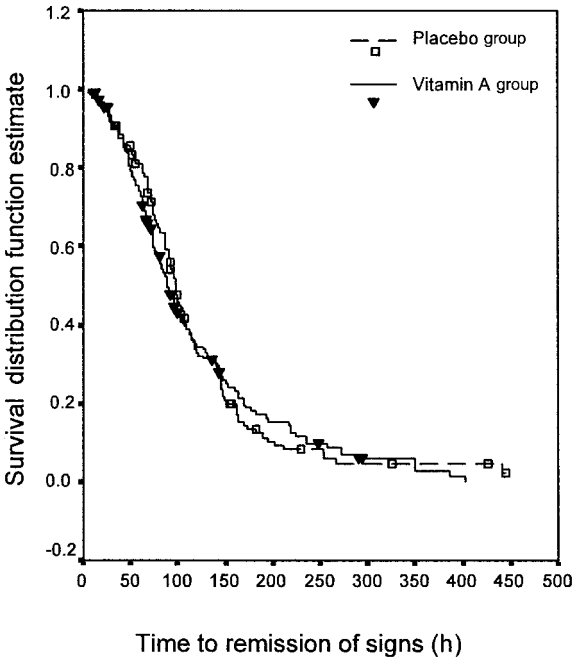

FIGURE 2. Kaplan-Meier survival curves for time to remission of all 3 signs of pneumonia. Log rank, P = 0.35

No previous reports have evaluated the effect of vitamin A supplements on the clinical evolution of pneumonia stratified by the severity of hypoxemia at enrollment. A study done in Brazil found an apparent beneficial effect of vitamin A on the clinical resolution of severe pneumonia, defined according to World Health Organization criteria (27). The World Health Organization's definitions of pneumonia do not include hypoxemia as an indicator of severity. In countries where substantial proportions of the population live at higher altitudes with reduced oxygen tension, the risk of hypoxemia associated with an episode is increased. In the current study, we encountered a trend toward faster resolution of clinical signs of pneumonia in children with oxygen saturation <80% at enrollment who were given placebo than in their counterparts who were given vitamin A. Although this was a post hoc analysis of a small number of subjects that is

TABLE 2
Duration of pneumonia manifestations[1]

	Vitamin A group (n = 121)	Placebo group (n = 118)
Tachypnea (h)	55.6 ± 52.1[2]	62.6 ± 61.8
Fever (h)	9.7 ± 14.61	11.1 ± 29.4
Hypoxemia (h)	101.4 ± 80.4	108.9 ± 100.5
Time to remission of all 3 signs (h)	106.7 ± 79.0	114.7 ± 107.5
Rales (d)	3.61 ± 2.28	4.06 ± 2.52
Diminished breath sounds (d)	1.24 ± 1.66	1.57 ± 1.8
Bronchial breath sounds (d)	0.26 ± 1.23	0.23 ± 0.99
Pleural effusion (d)	0.024 ± 0.27	0.03 ± 0.15
Resolution of focal infiltrate at 72 h (%)	25.3	27.8

[1] Differences were not significant. Data for percentages were analyzed with the chi-square test.
[2] $\bar{x}$ ± SD (all such values). Data were analyzed with Student's t test.

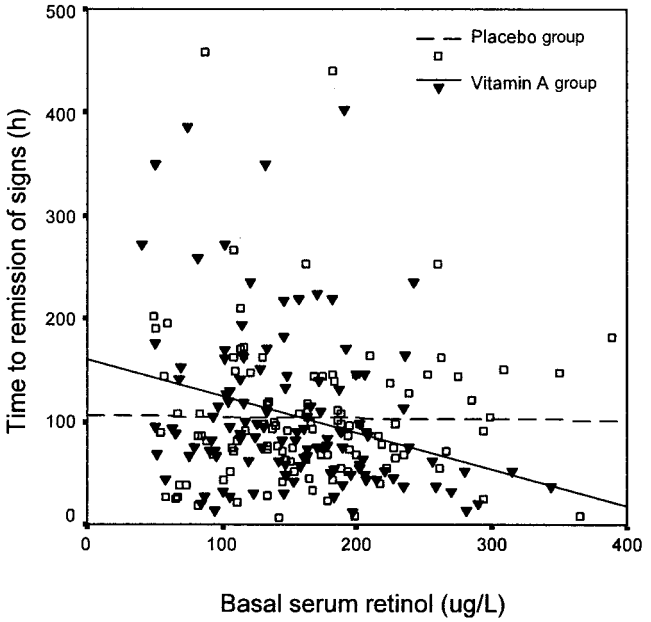

FIGURE 3. Correlation between time to remission of signs of pneumonia and basal serum retinol concentrations. A significant ($P = 0.001$) interaction was observed between baseline serum retinol (in μg/L) and vitamin A group.

potentially subject to bias, these findings may simply represent chance findings that may not be replicated in a follow-up study.

Although no overall effect of vitamin A on the duration of clinical manifestations of pneumonia was observed, we did observe that children with high basal serum retinol concentrations were more likely to have a faster resolution of clinical signs of pneumonia than were those with low concentrations. Moreover, vitamin A supplements shortened the clinical evolution in this group of children, but the number of subjects was small. In fact, a significant interaction was found between basal serum retinol and vitamin A supplementation. There are 2 potential explanations for these findings. First, these children may have been less severely ill and therefore might have had less depression of their serum retinol concentrations by the acute phase response. Second, the children who were better nourished at baseline in terms of their vitamin A status may have been better able to generate an effective immune response and to use the vitamin A supplement more efficiently to fight the infection and rebound more rapidly from the bout of pneumonia than were those who were less well nourished. Accordingly, because vitamin A deficiency is declining in increasing numbers of populations, more children could benefit from vitamin A supplements during a pneumonia episode. Then it would not seem necessary to assess the basal retinol status in children with pneumonia before giving them moderate doses of vitamin A supplements. In addition, no adverse events have been reported following the use of moderate doses of vitamin A. If these explanations are correct, then they underline the importance of continued public health interventions to reduce or eliminate both subclinical and clinical vitamin A deficiency. More studies are required to test these assumptions.

We thank Judy Irigoyen of the Ecuadorian National Research Institute of Health, Ana Delgado of UNICEF in Quito, and Christine Ayash of the Center for International Health and Development for logistic support. Recognition is due to Elena Naumova for statistical advice. We also appreciate the technical assistance of Anabel Medina and the personnel of the Radiology Department, Lucy Baldeon of the Emergency Room at Baca Ortiz Children's Hospital, and the following students from School of Medicine of the Central University of Ecuador: Eduardo Basantes, Francisco Benavides, Pablo Brito, Karina Calvas, Ramiro Cazar, Juan Carlos Cazar, Galo Fraga, Diego Granja, Fabricio Morales, and Veronica Plaza.

FS, AR, JR, and MA participated in the design and execution of the study and in the preparation of the manuscript. GS, MG, MC, CN-P, JL, DG, GF, EJ, and GG participated in the execution of the study and the preparation of the manuscript. DHH and BE participated substantially in the design of the study, analysis of the data, and preparation of the manuscript. None of the authors had a personal or financial conflict of interest.

REFERENCES

1. Mathers CD, Murray CJL, Lopez AD, Stein C. The global burden of disease 2000 project: objectives, methods, data sources and preliminary results. Evidence and information for policy (EIP). Geneva, Switzerland: World Health Organization, 2001.
2. Benguigui Y. Unidades de capacitación en el tratamiento de las infecciones respiratorias agudas. Control de las Infecciones Respiratorias Agudas: Implementación, Seguimiento y Evaluación. (Training units for the treatment of acute respiratory infections. Control of acute respiratory infections: implementation, follow-up, and evaluation.) Organización Panamericana de la Salud/Organización Mundial de la Salud. HCT/AIEPI-6, 1997 (in Spanish).
3. World Health Organization. Bases técnicas para las recomendaciones de la OPS/OMS sobre el tratamiento de la neumonía en el primer nivel de atención. (Technical bases for PAHO/WHO recommendations on the treatment of pneumonia in primary health care.) Geneva, Switzerland: World Health Organization (WHO/ARI), 1991 (in Spanish).
4. World Health Organization. Program for the Control of Acute Respiratory Infections. Program report, 1988. Geneva, Switzerland: World Health Organization (WHO/ARI), 1990.
5. Alvarez M, Cáceres L, Gavilanes G. Evaluación del Manejo de la IRA en menores de 5 años de los Centros y Subcentros urbanos del Ministerio de Salud Pública en Quito, Ecuador. (Evaluation of the management of acute respiratory infection in children under 5 years of age at urban health centers of the Ministry of Public Health in Quito, Ecuador.) In: Benguigui Y, Valenzuela C, eds. Investigaciones operativas sobre el control de las infecciones respiratorias agudas (IRA) en niños de América Latina y el Caribe. [Operative research on the control of acute respiratory infections (ARI) in Latin American and Caribbean children.] Buenos Aires, Argentina: Organización Panamericana de la Salud/Organización Mundial de la Salud. HCT/AIEPI-3.E, 1998:157–81 (in Spanish).
6. Benguigui Y. Magnitud y control de las IRA en función de las metas de la cumbre mundial de la infancia. (Magnitude and control of ARI according to the goals of the global summit on children.) In: Benguigui Y, López FJ, Schmunis G, Yunes J, eds. Infecciones respiratorias en niños. (Respiratory infections in children.) Washington, DC, Organización Panamericana de la Salud/Organización Mundial de la Salud. HCT/AIEPI-1, 1999:25–43 (in Spanish).
7. El Bushra HE, Ash LR, Coulson AH, Neuman CG. Interrelationship between diarrhea and vitamin A deficiency: is vitamin A deficiency a risk factor for diarrhea? Pediatr Inf Dis J 1992;11:380–4.
8. Bloem MW, Wedel M, Egger RJ, et al. Mild vitamin A deficiency and risk of respiratory tract diseases and diarrhea in preschool and school children in Northeastern Thailand. Am J Epidemiol 1990;131:332–9.
9. Milton RC, Reddy V, Naidu AN. Mild vitamin A deficiency and childhood morbidity: an Indian experience. Am J Clin Nutr 1987;46:827–9.
10. Sommer A, Katz J, Tarwatjo I. Increased risk of respiratory disease and diarrhea in children with pre-existing vitamin A deficiency. Am J Clin Nutr 1984;40:1090–5.
11. Hussey GD, Klein M. A randomized, controlled trial of vitamin A in children with severe measles. N Engl J Med 1990;323:160–4.
12. Barclay AIG, Foster A, Sommer A. Vitamin A supplements and mortality related to measles: a randomised clinical trial. Br Med J 1987;294:294–6.
13. Stallings RY, Kjolhede C, Dibley MJ, Sadjimin T. Environmental risk factors and incidence and duration of acute respiratory illness among children in a randomized field trial of vitamin A in central Java. FASEB J 1992;6:1649 (abstr).
14. West KP Jr, Katz J, Shrestha S, et al. Mortality of infants < 6 mo of age supplemented with vitamin A: a randomized, double-masked trial in Nepal. Am J Clin Nutr 1995;62:143–8.

15. Dibley MJ, Sadjimin T, Kjolhede CL, Moulton LH. Vitamin A supplementation fails to reduce incidence of acute respiratory illness and diarrhea in preschool-age Indonesian children. J Nutr 1996;126:434–42.
16. The Vitamin A and Pneumonia Working Group. Potential interventions for the prevention of childhood pneumonia in developing countries: a meta-analysis of data from field trials to assess the impact of vitamin A supplementation on pneumonia morbidity and mortality. Bull World Health Organ 1995;73:609–19.
17. Sempértegui F, Estrella B, Camaniero V, et al. The beneficial effects of weekly low dose vitamin A supplementation on the acute lower respiratory infections and diarrhea in Ecuadorian children. Pediatrics [serial online] 1999;104(1):e1. Internet: http://www.pediatrics.org/cgi/content/full/104/1/e1.
18. Julien MR, Gomes AC, Varandas L, et al. A randomized, double-blind, placebo-controlled clinical trial of vitamin A in Mozambican children hospitalized with nonmeasles acute lower respiratory tract infections. Trop Med Int Health 1999;4:794–800.
19. Nacul LC, Arthur P, Kirkwood BR, Morris SS, Cameiro AC, Benjamin AF. The impact of vitamin A supplementation given during a pneumonia episode on the subsequent morbidity of children. Trop Med Int Health 1998;3:661–6.
20. Fawzi WW, Mbise RL, Fataki MR, et al. Vitamin A supplementation and severity of pneumonia in children admitted to the hospital in Dar es Salaam, Tanzania. Am J Clin Nutr 1998;68:187–92.
21. Velasquez-Melendez G, Okani ET, Kiertsman B, Roncada MJ. Vitamin A status in children with pneumonia. Eur J Clin Nutr 1995;49:379–84.
22. Kjolhede CL, Chew FJ, Gadomski AM, Marroquin DP. Clinical trial of vitamin A as adjuvant treatment for lower respiratory tract infections. J Pediatr 1995;126:807–12.
23. Stephensen CB, Franchi LM, Hernandez H, Campos M, Gilman RH, Alvarez JO. Adverse effects of high-dose vitamin A supplements in children hospitalized with pneumonia. Pediatrics [serial online] 1998; 101:e3. Internet: http://www.pediatrics.org/cgi/coontent/full/101/5/e3.
24. Donnen P, Dramaix M, Brasseur D, Bitwe R, Vertongen F, Hennart P. Randomised placebo-controlled clinical trial of the effect of a single high dose or daily low doses of vitamin A on the morbidity of hospitalized, malnourished children. Am J Clin Nutr 1998;68:1254–60.
25. World Health Organization. Measuring change in nutritional status. Guidelines for assessing the nutritional impact of supplementary feeding programs for vulnerable groups. Geneva, Switzerland: World Health Organization, 1983.
26. Collett D. Modelling survival data in medical research. London, United Kingdom: Chapman & Hall, 1994.
27. World Health Organization. Acute respiratory infections in children: case management in small hospitals in developing countries. WHO/ARI/90.5. Geneva, Switzerland: WHO, 1990.
28. Kyran P, Quinlan KP, Hayani KC. Vitamin A and respiratory syncytial virus infection. Arch Pediatr Adolesc Med 1996;150:25–30.
29. Si NV, Grytter C, Vy NNT, Hue NB, Pedersen FK. High dose vitamin A supplementation in the course of pneumonia in Vietnamese children. Acta Paediatr 1997;86:1052–5.
30. Freire W, Dirren H, Mora JO, et al. Diagnóstico de la situación alimentaria, nutricional y de la salud de la población Ecuatoriana menor de cinco años–CONADE/MSP. (Diagnosis of the food, nutrition and health status of the Ecuadorian population under five years of age.) Quito, Ecuador: Namur Eds, 1988 (in Spanish).
31. Rodríguez A, Guamán G, Nelson D. Estado nutricional de los niños de cinco provincias de pobreza critica del Ecuador con respecto a la vitamina A. (Nutritional status of children from five poor provinces of Ecuador regarding vitamin A.) Boletín de la Oficina Sanitaria Panamericana 1996;120:117–24 (in Spanish).
32. Acosta M, Rodríguez A. Evaluación de la situación nacional de vitamina A en Ecuador. Impacto de los problemas nutricionales en la salud pública. (Evaluation of vitamin A situation in Ecuador. The impact of nutritional problems on public health.) Quito, Ecuador: CONUEP, 1996 (in Spanish).
33. Rosales FJ, Ritter SJ, Zolfaghari R, Smith JE, Ross AC. Effects of acute inflammation on plasma retinol, retinol-binding protein, and its mRNA in the liver and kidneys of vitamin-A sufficient rats. J Lipid Res 1996; 37:962–71.
34. Felding R, Fex G. Rates of synthesis of prealbumin and retinol-binding protein during acute inflammation in the rat. Acta Physiol Scand 1985; 123:477–83.
35. Gieng SH, Raila J, Rosales FJ. Accumulation of retinol in the liver after prolonged hyporetinolemia in the vitamin A-sufficient rat. J Lipid Res 2005;46:641–9.
36. Stephensen C, Alvarez J, Kohatsu J, Hardmeier R, Kennedy JJ, Gammon R. Vitamin A is excreted in the urine during acute infection. Am J Clin Nutr 1994;60:388–92.
37. Alvarez JO, Salazar-Lindo E, Kohatsu J, Miranda P, Stephensen CB. Urinary excretion of retinol in children with acute diarrhea. Am J Clin Nutr 1995;61:1273–76.
38. Stephensen C. When does hyporetinolemia mean vitamin A deficiency? Am J Clin Nutr 2000;72:1–2.
39. Rodríguez A, Guamán G, Mayorga E, et al. Situación de vitamina A–MRDR– en centros de desarrollo infantil de zonas urbano marginales de Quito y Guayaquil. (Situation of vitamin A -MRDR- in day care centers of urban slums in the cities of Quito and Guayaquil.) Quito, Ecuador: Ministerio de Salud Pùblica del Ecuador, 1995 (in Spanish).
40. Nacul LC, Kirkwood BR, Arthur P, Morris SS, Magalhaes M, Fink MC. Randomized, double blind, placebo controlled clinical trial of efficacy of vitamin A treatment in non-measles childhood pneumonia. BMJ 1997; 315:505–10.