Acute Respiratory Infections Prevent Improvement of Vitamin A Status in Young Infants Supplemented with Vitamin A[1,2]

M. MUJIBUR RAHMAN, D. MAHALANABIS,* J. O. ALVAREZ†[3] M. A. WAHED,* M. A. ISLAM,* D. HABTE*, AND M. A. KHALED†*

**International Centre for Diarrhoeal Disease Research, Bangladesh, and †Departments of International Health and Nutrition Sciences, University of Alabama at Birmingham, AL*

ABSTRACT At immunization contact, 165 infants 2.5 mo old were randomly assigned to receive either 15 mg vitamin A (retinyl palmitate) or placebo. Three doses were given at monthly intervals with each diptheria, pertussis, tetanus and oral polio (DPT/OPV) immunization dose. The diarrhea and acute respiratory infection (ARI) morbidity was similar in the vitamin A and placebo groups. However, the duration (days per child-year, mean ± SD) of ARI was less in the vitamin A group compared with placebo group (27.6 ± 17.1 vs. 40.8 ± 22.7; $P = 0.005$). Fasting retinol concentrations were measured at entry and in 61 infants, the relative dose response (RDR) test was done 1 mo after the third dose of vitamin A. Eighty-five percent of the infants had serum retinol concentration < 0.70 mol/L at entry. After 3 mo the serum retinol levels improved significantly in both groups, and in the vitamin A-supplemented group the serum retinol concentration was significantly better than that in the placebo group ($P = 0.02$). However, 61% of the infants remained deficient despite vitamin A supplementation. Among vitamin A-supplemented infants only, diarrhea and ARI morbidity during the 3-mo period were compared in children with normal versus children with abnormal RDR at the end of the supplementation period. The ARI episodes were more frequent in the supplemented infants who remained vitamin A deficient at the end of the 3 mo ($P = 0.027$). Also, the cumulative duration (days, mean ± SD) of fever and cough was 5.0 ± 2.8 in the normal versus 11.2 ± 6.0 in the deficient group ($P = 0.04$). The results of this study suggest that a large proportion of infants remain vitamin A deficient even after large dose vitamin A supplementation because of frequent respiratory infections, particularly those accompanied by fever. J. Nutr. 126: 628–633, 1996.

INDEXING KEY WORDS:

• *vitamin A* • *diarrhea* • *acute respiratory infection* • *fever* • *humans*

Mild vitamin A deficiency is associated with an increased rate of infections (Milton et al. 1987, Sommer et al. 1984), and large dose vitamin A supplementation has improved vitamin A status and reduced childhood mortality (Rahmatullah et al. 1990, Sommer et al. 1986, West et al. 1991). The expanded program on immunization (EPI)[4] has achieved remarkable success in raising the immunization coverage rate in developing countries. The EPI vaccine coverage rate in Bangladesh is >80% (UNICEF 1993). Because infants are born with low reserves of vitamin A (Olson et al. 1984), there is interest in initiating vitamin A administration at

[1] This research was supported by the United States Agency for International Development (USAID) under grant no. DPE-598-A-1009-00 with the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B). The ICDDR,B is supported by countries and agencies which share its concern for the health problems of developing countries. Current donors include: the aid agencies of the Government of Australia, Bangladesh, Belgium, Canada, China, Denmark, Germany, Japan, the Netherlands, Norway, Republic of Korea, Saudi Arabia, Sweden, Switzerland, the United Kingdom and the United States; international organizations including the Arab Gulf Fund, Asian Development Bank, International Atomic Energy Centre, the United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP), the United Nations Population Fund (UNFPA) and the World Health Organization (WHO); private foundations including the Ford Foundation, Population Council, Rockefeller Foundation and the Sasakawa Foundation; and private organizations including American Express Bank, Bayer Ag, CARE, Helen Keller International, the Johns Hopkins University, Swiss Red Cross, the University of California Davis, and the University of Alabama at Birmingham.

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[3] Reprint requests: J. O. Alvarez, Dept. of International Health, 106 TH, UAB, Birmingham, AL 35294-0008, USA.

[4] Abbreviations used: ARI, acute respiratory infections; BCG, Bacillus calmette guerin; DPT, diphtheria, pertussis, tetanus; EPI, expanded program on immunization; HPLC, high performance liquid chromatography; OPV, oral polio vaccine; RDR, relative dose response.

0022-3166/96 $3.00
Manuscript received 13 April 1995. Initial review completed 14 August 1995. Revision accepted 29 November 1995.

immunization contact. However, adverse side effects such as bulging fontanelle have raised concerns about the toxic effect of large dose supplements of vitamin A in infants (de Francisco et al. 1993, Rahman et al. 1995). Furthermore, the efficacy of this supplementation in young infants is not known. Recent studies in Bangladesh have shown that despite administration of three doses of 15 mg and 7.5 mg vitamin A at monthly intervals, in a large proportion of infants serum retinol levels remained low (Mahalanabis et al., unpublished data, Rahman et al. 1995). In this study we evaluated the postsupplementation vitamin A status in infants using the relative dose response (RDR) after three doses of 15 mg vitamin A given at monthly intervals at the time of immunization. We also examined the hypothesis that the postsupplementation (vitamin A) deficiency status is related to disease burden due to high diarrhea and respiratory infections.

SUBJECTS AND METHODS

This study was done in the EPI clinic of the Clinical Research and Service Centre of the International Centre for Diarrhoeal Diseases Research (ICDDR,B) in Dhaka, Bangladesh. In Bangladesh, the EPI schedule includes Bacillus calmette guerin (BCG) vaccination soon after birth; three doses of diphtheria, pertussis and tetanus (DPT) and oral polio (OPV) at 4-wk intervals starting at the age of 6 wk; measles vaccination at the age of 9 mo. Based on the missed opportunity concept (WHO 1989), all children under 2 y of age are vaccinated at this EPI Clinic when they are discharged (Islam et al. 1992). One hundred sixty-five infants 6–17 wk old of either sex attending the immunization clinic for their first DPT/OPV dose and who had just recovered from diarrhea were enrolled after consent from the parents. Infants with infections such pneumonia, diarrhea, septicemia and others were excluded from this study.

Sample size. The sample size was calculated to examine the efficacy of supplementation in improving vitamin A stores, to allow for morbidity comparison between vitamin A deficient and normal infants and to examine the toxic effects of vitamin A supplementation. A recent study in Bangladesh (Wahed et al. 1995) showed that prevalence of marginal vitamin A deficiency as measured by RDR was 61% among children aged 6–35 mo. We assumed that at least 40% of our infants receiving placebo (because our infants were younger than those children) would be deficient. The administration of three doses of 15 mg vitamin A should virtually eliminate the deficiency. However, we assumed that 5% of the supplemented infants would remain deficient. To detect this degree of difference at 5% level of significance with 90% power, the sample size in each group was required to be 25 (total 50). To evaluate the morbidity (diarrhea and ARI) among the RDR-positive and -negative cases with an odds ratio of 4.0, we required a sample size of 49 in each group (assuming prevalence of abnormal RDR = 0.4, significance level = 5% and power = 80%). For the toxic effect, the sample size required was 400 (assuming that 5% infants would have bulging fontanelle among supplemented infants). Thus the total sample size for this study was 400.

Study design. Infants were randomly assigned to receive either 15 mg vitamin A or placebo. Retinyl palmitate (15 mg) in oil made up into a liquid preparation and a placebo made from soybean oil in a liquid preparation were provided as individual doses in airtight dark bottles prepared by a local pharmaceutical company (ACME Laboratories, Bangladesh). The vitamin A content was verified by analysis using high performance liquid chromatography (HPLC, Waters, Millipore, Bedford, MA) at the beginning and at the end of the study. A randomization list was prepared by a senior staff member not directly involved in the study. Sets of three bottles containing vitamin A or placebo for each infant were serially numbered according to randomization. The randomized bottles were stored at 4°C before use. Initial randomization was done for 400 infants because the sample size calculated was 400 to evaluate the toxicity of vitamin A supplementation. However, because 10% of the infants receiving vitamin A developed bulging fontanelle during interim analyses, the supplementation study with 15 mg vitamin A stopped. A report on the side effects of vitamin A supplementation in this cohort of children has been submitted for publication elsewhere (Mahalanabis et al., personal communication).

After enrollment, vitamin A or placebo was fed to the infants according to randomization. Thereafter the child was immunized with the first doses of DPT and OPV. Second and third supplementation of vitamin A were given at 4 and 8 wk along with immunization. The children were followed up at home twice a month for diarrhea and acute respiratory infection (ARI) morbidity. Mothers were advised and motivated to bring their children for treatment of any illness to the hospital. Diarrhea was defined as three or more watery or liquid stools in 24 h or bloody mucoid stools. Fever, cough and hurried breathing as perceived by the mothers or examined by physician (during hospital visit) were recorded separately. For analysis those infants who were treated with antibiotics were coded as having ARI. Fever and cough irrespective of treatment with antibiotics were coded separately. Therefore, fever was common to both conditions. The number of episodes of illness and the duration of each episodes were recorded. A disease-free interval of 72 h was required to define a new episode.

Venous blood was drawn after a 6-h food deprivation to assay serum retinol at entry. One month after the third dose, relative dose-response test was done only in those infants whose mothers consented for blood drawing twice. For the RDR, 1000 g retinol palmitate

TABLE 1

Characteristics of the infants who received three doses of 15 mg vitamin A or placebo at monthly intervals at immunization

	Vitamin A (*n* = 84)	Placebo (*n* = 81)
Age at entry		
42–59 d/60–89 d/90–119 d, *n*	41/30/13	40/18/23
Mean ± SD, *d*	72.4 ± 20.5	75.2 ± 25.9
Sex: male/female	50/34	54/27
Breastfeeding: yes/no	73/11	73/8
Wt/age		
<60/60–74.9/75–89/90+, *n*	2/33/32/17	3/30/31/17
mean ± SD, % *NCHS median*	79.5 ± 11.8	79.8 ± 12.2
Family income		
<40/40–75/>75, *n*	27/34/23	26/40/15
Median (range), *$U.S./mo*	60 (20–375)	50 (10–300)
Serum retinol		
<0.35, *n* (%)	37 (45.1)	33 (41.8)
0.35–0.52, *n* (%)	16 (19.5)	21 (26.6)
0.525–0.795, *n* (%)	17 (20.7)	17 (21.5)
≥0.70, *n* (%)	12 (14.7)	8 (10.1)
Mean ± SD, *μmol/L*	0.43 ± 0.24	0.42 ± 0.20

was fed to the infants after taking 1 mL venous blood (baseline sample). After 5 h, a second blood sample was drawn. The samples were analyzed using HPLC for serum retinol. The RDR was calculated using the formula:

$$\text{RDR} = \frac{A_5 - A_0}{A_5} \times 100$$

where A_0 is the fasting retinol and A_5 is the serum retinol at 5 h. An RDR value ≥ 20 was defined as inadequate vitamin A stores, i.e., vitamin A deficiency (Flores et al. 1984). This study was approved by the ethical committee (ERC) of the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B).

Data analysis. Data analyses were done by the statistical package for Social Sciences SPSS/PC+ (Chicago, IL). Proportions were compared by χ^2 tests. The χ^2 for trend was calculated using EPI INFO packages (CDC, Atlanta, GA). The difference between means was tested by Student's *t*-test in normally distributed data, and the nonparametric (Mann-Whitney) test was used for skewed data. To adjust the effects of confounding factors on postdose vitamin A status, a multiple logistic regression analysis was done. Statistical significance was accepted at 5% probability level. Values in the text are means ± SD.

RESULTS

On admission, serum retinol concentrations were 0.43 ± 0.24 and 0.42 ± 0.20 mol/L in the vitamin A and placebo groups, respectively (**Table 1**). The baseline characteristics of the infants in the vitamin A group and the placebo group were comparable. **Tables 2** and **3** show the diarrhea and respiratory morbidity, respectively. There was no difference in the episodes per child-year of diarrhea between the vitamin A group and the placebo group, nor was there any difference in the duration (days per child-year) of diarrhea between the two groups. The ARI episodes (per child-year) were not significantly different in the two groups, but the ARI duration was significantly less in infants who received three doses of 15 mg vitamin A.

Table 4 shows the serum retinol concentrations before and after supplementation as well as the results of the RDR test after vitamin A supplementation. Post-supplementation RDR was done in 61 children. These infants were comparable with those who were not

TABLE 2

Diarrhea morbidity during 5-mo follow-up period in infants supplemented with 15 mg vitamin A

	Vitamin A group (*n* = 84)	Placebo group (*n* = 81)
Diarrhea episodes (per child-year)		
0	16	20
1–3	24	21
4–6	23	10
≥7	21	30
Mean ± SD, *d per child-y*	4.2 ± 3.2	4.7 ± 4.5
Diarrhea duration (days per child-year)		
0	16	20
1–10	13	14
11–20	19	16
>20	36	31
Mean ± SD, *d per child-y*	25.7 ± 17.0	29.7 ± 24.1

TABLE 3

Acute respiratory infections (ARI) morbidity during 5-mo follow-up period in infants supplemented with 15 mg vitamin A

	Vitamin A group (*n* = 84)	Placebo group (*n* = 81)
ARI episodes (per child-year)		
0	43	43
1–3	24	19
4–6	14	10
≥7	3	9
Mean ± SD, *d per child-y*	1.8 ± 2.3	2.0 ± 2.5
ARI duration (days per child-year)		
0	43	43
1–10	7	1
11–20	8	3
≥21	26	34
Mean ± SD, *d per child-y*	27.6 ± 17.1	40.8 ± 22.7[1]

[1] Significantly different from the vitamin A group; $P < 0.01$ (Mann-Whitney test).

TABLE 4

Vitamin A status of infants before and after monthly supplementation with three doses of 15 mg vitamin A or placebo

	Vitamin A (n = 33)		Placebo (n = 28)	
	Before[1]	After[2]	Before[3]	After[4]
Serum retinol				
<0.35	19	2	12	7
0.35–0.524	6	4	7	4
0.525–0.69	3	9	9	9
≥0.70	5	18	0	8
Mean ± SD, μmol/L	0.39 ± 0.26	0.74 ± 0.23[a]	0.37 ± 0.20	0.61 ± 0.28[b]
Relative dose response, n (%)				
≥20	—	20 (61)[c]	—	23 (82)[d]
<20	—	13 (39)	—	5 (18)

[1] vs. [2] χ^2 for trend = 22.68; $P < 0.0001$.
[1] vs. [3] χ^2 for trend = 0.082; $P = 0.77$.
[3] vs. [4] χ^2 for trend = 7.6; $P = 0.005$.
[2] vs. [4] χ^2 for trend = 6.6619; $P = 0.009$.
[a] vs. [b] $P = 0.02$ (Mann-Whitney test).
[c] vs. [d] $\chi^2 = 3.38$; $P = 0.06$.

tested for RDR. Of the 61 infants, 33 received vitamin A and 28 received placebo. Twenty-eight infants (85%) in the vitamin A group and all infants in the placebo group had serum retinol levels of <0.70 mol/L before supplementation (Table 4). The number of infants with fasting retinol < 0.35 mol/L was 19 (58%) in the vitamin A group and 12 (43%) in the placebo group (P = 0.15). After 3 mo the serum retinol level improved significantly in both groups, but the improvement was more evident in the vitamin A-supplemented group. As measured by the RDR test, 20 infants (61%) in the vitamin A group and 23 (82%) in the control group were still vitamin A deficient ($\chi^2 = 3.38$; $P = 0.06$) after supplementation.

Because our intention was to examine the association of morbidity with the postsupplementation vitamin A deficiency status, we compared the morbidity status of the infants who remained vitamin A deficient with those whose vitamin A stores were adequate after supplementation (see **Table 5**). The duration and episodes of diarrhea in the RDR normal infants at the end of the supplementation period were similar to those whose RDR were abnormal. However, ARI episodes were more frequent in those infants who remained deficient after receiving the vitamin A supplements (χ^2 for trend = 4.8; $P = 0.027$). The duration (days) of fever and cough was significantly shorter in infants with improved vitamin A status compared with those who did not improve ($P = 0.04$). A logistic regression analysis was done to adjust the effect of age, sex, family income and baseline serum retinol concentrations (not shown). The variables of interest were categorized using median value as cut up. The odds ratios (95% CI) of postdose vitamin A deficiency (RDR > 20) in vitamin A-supplemented infants were 5.4 (0.33–87.3; $P = 0.22$) for ARI episodes, 3.4 (0.15–70.8; $P = 0.42$) for duration of fever and cough, 7.1 (1.02–49.4; $P = 0.04$) for baseline retinol concentration, 1.2 (0.17–8.9); $P = 0.8$) for age and 4.4 (0.59–32.4; $P = 0.14$) for family income. The adjusted odds ratios for ARI episodes and duration were high. However, these were not statistically significant (wide 95% CI) because of the small number of subjects in each subgroup.

TABLE 5

Relative dose-response (RDR) test values and morbidity among vitamin A-supplemented infants during a 3-mo follow-up period

	Relative dose response	
	Normal (n = 13)	Abnormal (n = 20)
Diarrhea episodes		
0	3	6
1	5	5
≥2	5	9
Cumulative days with diarrhea		
0	3	6
1–5	2	5
6–9	4	4
10+	4	5
Mean ± SD, d	9.4 ± 5.0	8.7 ± 5.4
Acute respiratory infections[1]		
0	12	12
1	1	2
≥2	0	6
Cumulative days with fever + cough		
0	8	8
1–5	2	2
6–9	3	4
10+	0	6
Mean ± SD, d	5.0 ± 2.8	11.2 ± 6.0[2]

[1] χ^2 for trend = 4.8; $P = 0.027$.
[2] $P < 0.05$ (Mann-Whitney test).

DISCUSSION

At recruitment when infants were 2.5 mo old, 85% of the infants studied had serum retinol levels < 0.70 mol/L, and their mean serum retinol was 0.42 mol/L. These low values confirm previous reports suggesting that human infants are born with low reserves of vitamin A in the liver (Olson et al. 1984). Because the prevalence of low birth weight in Bangladesh is as high as 50% (UNICEF 1993), it is conceivable that a large proportion of the infants participating in this study were low birth weight babies and thus born with very low vitamin A stores (Neel and Alvarez 1990). The birth weights of our study infants were not recorded. At the end of the 3-mo follow-up period, the mean serum retinol improved in both groups (see Table 4). This was expected because liver stores of vitamin A build up during the first 6 mo of life (Olson et al. 1984). Nonetheless, the difference in serum retinol level between the vitamin A-supplemented and the placebo group, although small, was significant. Also, 82% of the placebo group had low vitamin A stores versus only 61% in the vitamin A-supplemented group as measured by RDR.

Because these children had just recovered from acute diarrhea, an alternative explanation to just being born with very low vitamin A stores is that their low serum retinol concentrations could be a transient suppression due to the diarrhea. A baseline RDR test would have been the best way to measure liver stores of vitamin A but could not be done in infants so young. However, RDR was done at the end of the 3-mo follow-up period (at the age of 5–6 mo). A large proportion of infants in both groups were still vitamin A deficient as measured by the RDR, suggesting that most of these infants had likely been born with low vitamin A stores (see Table 5).

Surprisingly, even after administration of three doses of 15 mg vitamin A at monthly intervals during a 3-mo period, 61% of the infants were still vitamin A deficient. Respiratory tract infection was found to be associated with this inadequate vitamin A status. Increased vitamin A requirement and catabolic loss of nutrients during ARI and fever may have substantially contributed to their deficient vitamin A status. Recent studies have shown that during acute infections, particularly those accompanied by fever, retinol is excreted in substantial amounts in the urine (Alvarez et al. 1995; Stephensen et al. 1994). It is likely that urinary loss of retinol in the infants with more frequent febrile episodes and respiratory infections was an important factor that contributed to their vitamin A-deficient status even after receiving a three-dose supplementation.

In developing countries, acute infections including measles, respiratory infections and diarrhea have been associated with increased risk of developing vitamin A deficiency in children (Bhaskaram et al. 1984, Feachem 1987, Reddy et al. 1986). Several longitudinal and cross-sectional studies conducted in India, Bangladesh and Tanzania have shown that after an acute attack of measles, vitamin A stores are severely depleted (Cohen et al. 1985, Foster and Sommer 1987, Khan et al. 1984, Reddy et al. 1986). Campos et al. (1987) showed that even a single episode of chicken pox infection in Brazilian children was associated with vitamin A depletion. On the other hand, vitamin A deficiency has been associated with increased mortality and morbidity in children (Milton et al. 1987, Sommer et al. 1984). In the present study, the children with more episodes of respiratory infections were vitamin A deficient despite receiving supplementation. This finding strengthens the notion that acute and recurrent infections are an important contributor to the development of vitamin A deficiency in children.

No reduction in the number of episodes and duration of diarrhea by vitamin A supplements was observed in the present study. The episodes of respiratory infection were also similar in the vitamin A-supplemented and placebo infants. These findings are consistent with previous findings of the studies done in India in children aged 6 mo–6 y (Bhandari et al. 1994; Rahmatullah et al. 1991). However, the cumulative days with respiratory infections were significantly less in the infants who received three doses of 15 mg vitamin A. A very recent study showed that with the standard definition of diarrhea (≥3 liquid or loose stools in 24 h), the effect of vitamin A in reducing diarrheal prevalence was not significant, but as the definition was made more stringent (>6 stools in 24 h), a significant reduction was apparent (Barreto et al. 1994). Thus, the beneficial effect of vitamin A supplementation is primarily seen as a reduction in the severity and duration of disease.

In this study the number of episodes of both diarrhea and ARI was higher than in other reports. The number of diarrhea episodes (per child-year) was 4.6, which is higher than the estimated global figure (3.1) for infants aged 6–11 months (Snyder 1982). Also, the number of respiratory infections was higher in our study population than in other studies in India and Indonesia. In our study the rate of ARI episodes (per child-year) was ~2, whereas it was only 0.85 in India and 0.14 in Indonesia (Milton et al. 1987). However, those children were older than these infants. The high frequency of infections (diarrhea and ARI) among infants of this study could be responsible for the lack of improvement in the vitamin A stores despite the three doses of 15 mg vitamin A given at monthly intervals.

In summary, the results of this study indicate that Bangladeshi infants unlike infants in developed countries remained vitamin A deficient by age 6 mo. Early vitamin A supplementation showed a beneficial effect only in reducing the duration of ARI. In a large proportion of these infants, vitamin A status did not improve even after three large doses of vitamin A administration. Acute respiratory infection and fever were strongly associated with a deficient vitamin A status in postsupplemented infants. Likely causes of sustained

vitamin A deficiency after three doses of 15 mg vitamin A are increased catabolism of the vitamin A or the high rate of retinol excretion in the urine that accompanies frequent infections in these infants.

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