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Respiratory infections reduce the growth response to vitamin A supplementation in a randomized controlled trial

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Background Studies on the effect of vitamin A supplementation on growth have yielded various results. It is possible that such growth is dependent on the burden of infectious diseases in the population.

Methods We analysed data from a randomized, double-masked, placebo-controlled trial to examine the role of respiratory infections and diarrhoea in modifying the growth response to vitamin A supplementation. A single high dose of vitamin A or placebo was given every 4 months to 1405 children aged 6–48 months, and 4430 child treatment cycles were used in this analysis.

Results Vitamin A supplementation modestly improved linear but not ponderal growth of children who experienced little respiratory infection and especially of those who had vitamin A intake below the normative requirement (<400 RE/day). Children who received vitamin A and were free of respiratory infection grew 0.22 cm/4 months (95% CI : 0.08, 0.37) more in height than the placebo group, but those with ⩾21.5% of days of respiratory infection did not show a significant growth response to vitamin A supplementation. Children who experienced no respiratory infection and had vitamin A intake <400 RE/day benefited most, gaining 0.31 cm/4 months (95% CI : 0.10, 0.52) more in height compared to the placebo group. Diarrhoea was associated with poorer growth, but did not significantly modify the effect of vitamin A supplementation on growth.

Conclusions Vitamin A supplementation improves the linear growth of children who have a low intake of vitamin A but this impact is muted with increasing levels of respiratory infections.

Keywords Vitamin A, growth, preschool children, respiratory infection, diarrhoea

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Studies on the effect of vitamin A supplementation on growth have yielded a variety of results, including modest benefits to growth[1,2] and no growth response.[3] It is possible that in these studies the impact of vitamin A has been modified by the burden of infectious disease in the communities. Previous studies have not investigated the role of infectious disease on the growth response to vitamin A.

There are several reasons to expect that infectious diseases may modify the growth response to vitamin A supplementation. Xerophthalmia, a clinical sign of vitamin A deficiency, is more likely to occur following respiratory tract infections[4,5] and diarrhoea;[4,6] the most common infectious diseases in preschool children in developing countries. Serum vitamin A levels decline in a variety of infections,[7,8] and the degree of decline is related to the severity and duration of the infection.[7] In respiratory infection, serum vitamin A levels are usually depressed,[7,9] due in part to an increased loss of vitamin A via urine,[10] or to a non-specific response to fever.[7,11] This fall in serum vitamin A levels may persist for days after the temperature has returned to normal.[7]

In respiratory infection, the absorption of vitamin A falls by as much as 74%.[12] Beta-carotene absorption may also fall by 50–80%, and continue at this level until 2 weeks after the last day of fever.[13] Absorption of vitamin A and beta-carotene is also impaired by gastrointestinal infections, especially in chronic

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salmonellosis[14] and when complicated by steatorrhoea.[9] Even in asymptomatic infection with parvovirus and certain strains of *Escherichia coli*, the absorption of vitamin A was also reduced.[15] Thus, the effect of vitamin A supplementation on child growth may depend upon the burden of infectious diseases in the population, which may influence the absorption, utilization and excretion of the supplemental vitamin A. Although children with more respiratory infections and diarrhoea are at most risk of vitamin A deficiency, we would expect that children with less respiratory infection and/or diarrhoea are more likely to benefit more from vitamin A supplementation, especially those with low vitamin A intake. We analysed data from a randomized controlled trial in which anthropometric, dietary vitamin A intake, and morbidity data were available, to determine if diarrhoea and respiratory infections influenced child growth and modified the growth response to vitamin A supplementation.

Materials and Methods

Study population and design

We analysed data from the MORVITA trial which was designed to investigate the effect of vitamin A on childhood morbidity, especially respiratory infection and diarrhoea. Details of the study design and the impact of vitamin A on morbidity are described elsewhere,[16] but important aspects of the trial methods are summarized below. The trial was implemented by the Johns Hopkins University in collaboration with the Faculty of Medicine, University of Gadjah Mada from 1989 to 1992. Two rural sub-districts, located on the southern coast of Central Java, Indonesia were selected as the study sites. In these communities a randomized, double-masked, placebo-controlled trial was conducted in which the treatments were given once every 4 months for six treatment cycles. Treatments containing either 214 μmol (206 000 IU) of vitamin A (or 107 μmol vitamin A if <12 months of age) or placebo were randomly assigned at the individual level to 1405 children who were aged 6–47 months at the start of each treatment cycle and this assignment remained fixed for all subsequent treatment cycles. Data were collected on 4430 child treatment cycles: 2178 from the placebo group and 2252 from the vitamin A group.

The protocol was reviewed and approved by the Committee on Human Research of the Johns Hopkins University School of Hygiene and Public Health, the Indonesian Vitamin A Research Steering Committee, and the Committee of Ethics in Human Biomedical Research of the Faculty of Medicine, University of Gadjah Mada. Written informed consent was obtained from the guardians of all children before entering the study. A programme of community education and meetings with the village headmen was conducted to help people understand the advantages and disadvantages of participating in the trial.

Data collection procedures

Anthropometric data

The child's weight and height were measured by a team of trained anthropometrists. Weight was measured every month in the integrated village health services post, while recumbent length or standing height was measured only every 4 months at the start of each cycle in the trial treatment clinic. If the child did not attend the post or clinic, the anthropometric team measured their weight and height at home.

Morbidity data

The child's morbidity experience was assessed by trained interviewers who visited the children and their guardians every other day to record symptoms of diarrhoea and respiratory illnesses. If the child was absent the interview was attempted at the next scheduled home visit. The longest recall period allowed was 4 days. These morbidity data were collected using Javanese language, on standardized pre-coded forms which had been developed by an anthropologist using focus group discussions and in-depth interviews with village women prior to the data collection.

Episodes of diarrhoea were defined as adjoining days for which the child was reported to have ⩾3 loose stools per 24-h period and ended if there were two or more symptom-free or missing data days. Episodes of respiratory illness were defined as ⩾2 adjoining days for which the child was reported to have cough and ended if there were ⩾3 symptom-free or missing data days.

Dietary vitamin A intake

A food frequency questionnaire was used to characterize the habitual vitamin A intake of individual children. A one-month recall period was used because the diets of young children change rapidly and because of the seasonal availability of many foods in the study area. The food frequency questionnaire was completed by high school graduates who were trained and supervised by nutritionists. These supervisors were also responsible for field editing of dietary intake forms. Interviews were conducted on the same day or within 2 days of the child's treatment cycle except for the first cycle where 30% of the interviews were conducted about one month after the trial treatment clinic.

Data management and statistical analysis

Pre-coded forms with preprinted identification labels were used for data collection. Data forms were edited by field supervisors before data entry and then entered into computers by trained operators using dSurvey[17] software. Statistical analyses were completed using SAS 6.11 (SAS Institute, Cary, NC) and STATA 5.0 (STATA Corporation, TX) software. Anthropometric indicators were calculated using the World Health Organization international growth reference[18] with computer subroutines provided by the US Center for Disease Control. Stunting was defined as having height for age Z-scores <–2 and weight for height Z-scores ⩾–2, while wasting was defined as having weight for height Z-scores <–2 and height for age Z-scores ⩾–2 based on the Waterlow malnutrition classification.[19]

Because most children contributed more than one treatment cycle to the analysis, Generalized Estimating Equations[20,21] were used in the analysis to account for the correlation of the repeated responses within individuals, and to allow full use of data from all 4430 child treatment cycles.

The outcome variable of this analysis was the 4-month height or weight increment. The explanatory variables included treatment, age, sex, percentage of days of respiratory infection, percentage of days of respiratory infection with elevated temperature, percentage of days of diarrhoea, dietary vitamin A intake, initial nutritional status, and season. Since children received different age-specific doses of vitamin A over the course of the study, all models in this analysis were adjusted for the cumulative dose of

vitamin A in international units. This cumulative dose reflected the total dose of vitamin A that had been received by each individual prior to a cycle-specific treatment. The trial treatment was handled as a categorical variable: vitamin A or placebo. Age was handled as a continuous variable. Vitamin A intake was handled as a dichotomous variable: below or above the normative requirement (>400 RE/day). Percentage of days with respiratory infection was divided into five categories and handled as four dummy variables: without respiratory infection, <25th percentile, 25–49th percentile, 50–74th percentile, and ⩾75th percentile of the respiratory infection distribution. Similarly the percentage of days of respiratory infections with elevated temperature and diarrhoea were divided into five categories by the same method. Season was grouped into three different seasons and handled as two dummy variables: season1 (December–March), season2 (April–July), and season3 (August–November). Both the main effect and the treatment interactions of the explanatory variables were considered. An SAS macro for longitudinal analysis, the GEE macro version 2.02,[22] was used in the analysis.

To test whether respiratory infection in combination with vitamin A intake modified the effect of vitamin A supplementation, children were stratified into two levels of vitamin A intake (above or below 400 RE/day) and three levels of respiratory infection (no respiratory infection, with <21.5% of days with respiratory infection, or ⩾21.5% of days with respiratory infection). The cutoff of 21.5% of days with respiratory infection was used because it was the 75th percentile of that distribution and because there was no difference in the growth response to vitamin A at levels below this. This stratification resulted in six different combinations of levels of vitamin A intake and respiratory infection. These new variables (termed RIVA) were treated as five dummy variables and included in the model with their corresponding interaction terms with treatment.

Results

Characteristics of the treatment groups

Details of characteristics of the two treatment groups are described elsewhere,[16] but briefly they had similar distributions of demographic, nutritional, and socioeconomic characteristics. The study population was characterized by a high prevalence of subclinical vitamin A deficiency with 52% having a serum retinol of 0.35–0.70 μmol/l and 15.4% with serum retinol of <0.35 μmol/l. However, only one child with a Bitot's spot had any evidence of clinical vitamin A deficiency.

Forty per cent of the study population had vitamin A intake above the normative requirement for vitamin A (>400 RE/day), 31% had vitamin A intake between the basal and the normative requirement (200–400 RE/day), and 29% of the children had daily vitamin A intake below the basal requirement (<200 RE/day) according to WHO standards.[23] Vitamin A intake differed by age. In children <24 months the mean was 290 ± 239 RE/day (mean ± SD), while in children ⩾24 months the mean was 485 ± 292 RE/day ($P < 0.0001$).

Overall, the mean percentage of days of respiratory infection was 14.0% ± 13.7% (mean ± SD), and the highest levels were found during the first year of life but then declined dramatically in linear fashion as age increased. The mean percentage of days of respiratory infection among children <24 months was 4.0% higher (95% CI : 3.2, 4.8%) compared to that among children ⩾24 months. Dibley *et al.*[16] have previously reported an excess in the vitamin A treated group of 8% (95% CI : 0.7–19%) in the incidence of respiratory infection but no difference in the duration of respiratory infection. Overall, the mean percentage of days of diarrhoea was 0.4% ± 1.2% (mean ± SD) and the age pattern was almost the same as for respiratory infections. The mean percentage of days of diarrhoea among children <24 months was 0.34% higher (95% CI : 0.27, 0.41%) compared to that among children ⩾24 months. There was no significant difference in the incidence or duration of diarrhoea between the vitamin A and the placebo groups.[16]

Effect of respiratory infection on growth and on growth response to vitamin A supplementation

Respiratory infection was not significantly associated with the growth of the children in the study (Table 1). There was no difference in height and weight increments between children with no respiratory infection versus those children with a progressively higher proportion of days with respiratory infection. However, respiratory infection did modify the effect of vitamin A supplementation on height increment but not on weight increment. Children receiving vitamin A with no respiratory infection gained 0.22 cm/4 months (95% CI : 0.08, 0.37) more in height than the placebo group. The growth response to vitamin A observed in those children who experienced <21.5% of days of respiratory infection was similar to the effect in children free of respiratory infection. In contrast, children receiving vitamin A but who experienced ⩾21.5% of days of respiratory infection, gained only 0.06 cm/4 months (95% CI : –0.06, 0.18) more in height than the placebo group. This height increment was 0.17 cm/4 months (95% CI : 0.002, 0.33) less than the height increment among children with no respiratory infection who were treated with vitamin A. Lastly, chronic cough, defined as more than 14 contiguous days of cough, did not affect growth, nor did it modify the effect of high dose vitamin A supplementation on growth (data not shown).

Effect of respiratory infection with elevated temperature (37.5°C) on growth and growth response to vitamin A supplementation

Respiratory infection with elevated temperature (⩾37.5°C) was not associated with the linear growth of the children in the study (Table 2). However respiratory infections with elevated temperature did modify the effect of vitamin A supplementation on height increment but not on weight increment. Children receiving vitamin A supplementation with respiratory infection but no elevated temperature gained 0.13 cm/4 months (95% CI : 0.04, 0.21) more than the placebo group (Table 2). In contrast, children who experienced 12.3% of days of respiratory infections with elevated temperature grew 0.10 cm/4 months (95% CI : –0.36, 0.16) less than the placebo group. This height increment was 0.23 cm/4 months (95% CI : 0.01, 0.44) less than the height increment among supplemented children with respiratory infection but no elevated temperature. The growth response of children with <12.3% of days of respiratory infections with elevated temperature was essentially the same as for children with respiratory infections but no elevated temperature.

Unlike height increment, weight increment was affected by episodes of respiratory infection with elevated temperature. As the percentage of days of respiratory infection with elevated

Table 1 The effect of vitamin A supplementation on 4-month height and weight increments of Indonesian preschool children by percentage of days with respiratory infection

	Outcome variables					
	Height increment			Weight increment		
Explanatory variables	β[a]	SE[b]	*P*-value[c]	β[a]	SE[b]	*P*-value[c]
Intercept	3.75	0.066	0.0000	0.67	0.026	0.0000
Treatment						
Vitamin A	0.22	0.073	0.0022	–0.03	0.030	0.2585
Placebo	–			–		
Respiratory infection (% days ill)						
RI_1 (0)	–			–		
RI_2 (<6.7)	0.04	0.066	0.5460	0.01	0.028	0.7604
RI_3 (6.7–12.4)	–0.07	0.065	0.2655	–0.04	0.025	0.1256
RI_4 (12.5–21.4)	–0.07	0.063	0.2394	–0.04	0.026	0.1442
RI_5 (≥21.5)	–0.02	0.064	0.8085	–0.04	0.025	0.1473
Treatment*RI_1	–			–		
Treatment*RI_2	–0.08	0.096	0.4122	0.04	0.039	0.3057
Treatment*RI_3	–0.08	0.091	0.3545	0.04	0.037	0.2340
Treatment*RI_4	–0.07	0.088	0.4600	0.06	0.038	0.1351
Treatment*RI_5	–0.17	0.083	0.0463	0.03	0.036	0.4670

[a] Regression coefficients.

[b] Robust standard errors.

[c] Robust *P*-values obtained from the Generalized Estimating Equations (GEE) adjusted for the within-child correlation, age, sex, vitamin A intake, initial anthropometric status, season, and cumulative doses.

Table 2 The effect of vitamin A supplementation on 4-month height and weight increments of Indonesian preschool children by percentage of days with elevated temperature during episodes of respiratory infection

	Outcome variables					
	Height increment			Weight increment		
Explanatory variables	β[a]	SE[b]	*P*-value[c]	β[a]	SE[b]	*P*-value[c]
Intercept	3.69	0.064	0.0000	0.64	0.022	0.0000
Treatment						
Vitamin A	0.13	0.044	0.0044	0.02	0.018	0.2951
Placebo	–			–		
Respiratory infection with elevated temperature (% days ill)						
ET_1 (0)	–			–		
ET_2 (<5.0)	–0.06	0.090	0.5093	–0.01	0.037	0.8450
ET_3 (5.0–8.2)	–0.04	0.096	0.6589	–0.06	0.035	0.0666
ET_4 (8.2–12.2)	–0.09	0.090	0.3450	–0.08	0.033	0.0161
ET_5 (≥12.3)	–0.05	0.097	0.6112	–0.09	0.036	0.0104
Treatment*ET_1	–			–		
Treatment*ET_2	0.09	0.127	0.4842	0.05	0.049	0.3565
Treatment*ET_3	0.04	0.126	0.7606	0.03	0.047	0.5499
Treatment*ET_4	–0.10	0.119	0.3943	–0.001	0.048	0.9885
Treatment*ET_5	–0.23	0.111	0.0351	–0.07	0.060	0.2602

[a] Regression coefficients.

[b] Robust standard errors.

[c] Robust *P*-values obtained from the Generalized Estimating Equations (GEE) adjusted for the within-child correlation, age, sex, vitamin A intake, initial anthropometric status, season, and cumulative doses.

temperature increased the gain in weight decreased. Children who experienced 5% of days of respiratory infections with elevated temperature gained about 64–93 g/4 months less in weight than those children free of respiratory infections with elevated temperature (Table 2). However, vitamin A supplementation had no significant effect on the weight increment of the children with respiratory infections with elevated temperature.

Table 3 The effect of vitamin A supplementation on 4-month height and weight increments of Indonesian preschool children by percentage of days with respiratory infection and vitamin A intake.

	Outcome variables					
	Height increment			Weight increment		
Explanatory variables	β[a]	SE[b]	*P*-value[c]	β[a]	SE[b]	*P*-value[c]
Intercept	3.68	0.083	0.0000	0.65	0.032	0.0000
Treatment						
Vitamin A	0.31	0.107	0.0045	–0.02	0.042	0.5601
Placebo	–			–		
RIVA (Respiratory infection & vitamin A intake)						
$RIVA_1$ (RI = 0 & VA <400 RE)	–			–		
$RIVA_2$ (RI <21.5% & VA <400 RE)	0.03	0.078	0.7133	–0.02	0.030	0.4374
$RIVA_3$ (RI ⩾21.5% & VA <400 RE)	0.02	0.089	0.8167	–0.02	0.033	0.5926
$RIVA_4$ (RI = 0 & VA ⩾400 RE)	0.14	0.098	0.1427	0.03	0.040	0.4001
$RIVA_5$ (RI <21.5% & VA ⩾400 RE)	0.04	0.079	0.5929	0.001	0.030	0.9774
$RIVA_6$ (RI ⩾21.5% & VA ⩾400 RE)	0.10	0.094	0.3073	–0.03	0.037	0.4442
Treatment*$RIVA_1$	–			–		
Treatment*$RIVA_2$	–0.19	0.114	0.0981	0.06	0.045	0.1906
Treatment*$RIVA_3$	–0.23	0.126	0.0647	–0.01	0.050	0.8428
Treatment*$RIVA_4$	–0.16	0.141	0.2615	–0.02	0.058	0.7218
Treatment*$RIVA_5$	–0.14	0.115	0.2385	0.03	0.045	0.5179
Treatment*$RIVA_6$	–0.25	0.116	0.0317	0.06	0.055	0.2855

[a] Regression coefficients.

[b] Robust standard errors.

[c] Robust *P*-values obtained from the Generalized Estimating Equations (GEE) adjusted for the within-child correlation, age, sex, vitamin A intake, initial anthropometric status, season, and cumulative doses.

Effect of respiratory infection in combination with vitamin A intake on growth response to vitamin A supplementation

There were no significant differences in height and weight increments between children grouped by respiratory infection and levels of vitamin A intake (RIVA, Table 3). However, the effect of vitamin A supplementation on linear and not on ponderal growth was modified by RIVA. Children with no respiratory infection and vitamin A intake <400 RE/day ($RIVA_1$), who received supplemental vitamin A gained 0.31 cm/4 months (95% CI : 0.10, 0.52) more in height than the placebo group. As days ill with respiratory infection and dietary vitamin A intake increased, children exhibited less linear growth response to the vitamin A supplementation. The weakest effect of vitamin A supplementation on height increment was found among children who had vitamin A intake ⩾400 RE/day and who experienced ⩾21.5% ($RIVA_6$) of days of respiratory infection; their linear growth response was reduced by 0.25 cm/4 months in comparison to children with no respiratory infection and vitamin A intake <400 RE/day.

Effect of diarrhoea on growth and on growth response to vitamin A supplementation

Unlike respiratory infection, diarrhoea adversely affected the growth of the children in the study (Table 4). Children who experienced diarrhoea during study intervals achieved smaller height increments than children who did not experience diarrhoea. As the percentage of days with diarrhoea increased the gain in height decreased, though the differences were not always statistically significant. Children with ⩾2.5% of days with diarrhoea grew 0.20 cm/4 months (95% CI : 0.03, 0.36) less in height than those children with no diarrhoea.

The effect of diarrhoea on weight increment was not as strong as its effect on height increment. Children with more days ill with diarrhoea were not statistically different in their weight gain from children with no diarrhoea (Table 4). The effect of vitamin A supplementation on height and weight increments did not vary with the percentage of days with diarrhoea.

Discussion

In previous studies, some investigators have found that vitamin A supplementation improved linear,[1,24] or ponderal growth,[2] but others found no effect.[3,25] Among those reporting a positive effect, older children benefited more in height[1] or weight[2] from vitamin A supplementation than younger children.

We have previously reported that vitamin A supplementation improved linear growth in this population, but the effect was modified by age, initial vitamin A status, and breastfeeding.[26] The mechanisms behind the age effects were not clear. However,

Table 4 The effect of vitamin A supplementation on 4-month height and weight increments of Indonesian preschool children by percentage of days with diarrhoea

	Outcome variables					
	Height increment			Weight increment		
Explanatory variables	β[a]	SE[b]	*P*-value[c]	β[a]	SE[b]	*P*-value[c]
Intercept	3.75	0.050	0.0000	0.65	0.018	0.0000
Treatment						
Vitamin A	0.14	0.041	0.0005	0.02	0.016	0.3632
Placebo	–			–		
Diarrhoea (% days ill)						
$Diarrhoea_1$ (0)	–			–		
$Diarrhoea_2$ (<0.85)	–0.02	0.089	0.7873	–0.004	0.031	0.9069
$Diarrhoea_3$ (0.85–1.60)	–0.07	0.087	0.4255	0.01	0.030	0.7331
$Diarrhoea_4$ (1.61–2.49)	–0.08	0.085	0.3295	–0.02	0.033	0.5394
$Diarrhoea_5$ (≥2.50)	–0.20	0.084	0.0199	–0.05	0.034	0.1249
Treatment*$Diarrhoea_1$	–			–		
Treatment*$Diarrhoea_2$	–0.06	0.122	0.6384	–0.01	0.045	0.8504
Treatment*$Diarrhoea_3$	0.04	0.136	0.7515	–0.04	0.050	0.4682
Treatment*$Diarrhoea_4$	–0.03	0.127	0.8091	–0.03	0.045	0.5464
Treatment*$Diarrhoea_5$	0.06	0.115	0.5882	–0.02	0.048	0.6581

[a] Regression coefficients.

[b] Robust standard errors.

[c] Robust *P*-values obtained from the Generalized Estimating Equations (GEE) adjusted for the within-child correlation, age, sex, vitamin A intake, initial anthropometric status, season, and cumulative doses.

respiratory infection and diarrhoea were less prevalent in older children, the group with the largest growth response to vitamin A supplementation. Our findings indicate that the growth-potentiating effect of vitamin A supplementation occurs only in children with a low burden of respiratory infection, and especially in those children with low vitamin A intakes. These results suggest biological mechanisms for the greater growth effect of vitamin A supplementation in older children.

Our findings indicate that respiratory infection defined by the presence of cough does not significantly affect growth; however, it does modify the effect of vitamin A supplementation on linear growth. Children who experienced respiratory infections for ≥26 days during a 4-month observation period had a 74% reduction (0.17 cm/4 months) in their linear growth response to vitamin A supplementation in comparison to children with no respiratory infection. In these children vitamin A supplementation did not significantly improve their linear or ponderal growth. It appears that respiratory infections interfere with the metabolism of vitamin A such that it is not available for improved growth. This could be because the vitamin A is not completely absorbed,[12] or is excreted in higher quantities during respiratory infection,[10] or it might be due to a non-specific response to fever during respiratory infections.[7,11] Any of these mechanisms would result in a smaller quantity of vitamin A being available for growth due to higher nutrient utilization.[7,11]

When fever was included in the definition of respiratory infection, we observed a 44% reduction in the linear growth response to vitamin A in children with respiratory infection but no elevated temperature in comparison to the placebo group (0.13 cm compared to 0.22 cm/4 months). Moreover, children who experienced ≥12.3% of days of respiratory infection with elevated temperature demonstrated no growth response to vitamin A supplementation in comparison to the placebo group. These observations are consistent with recent findings from a randomized controlled trial in which vitamin A supplementation did not improve the vitamin A status of young infants with a high burden of respiratory infection.[27]

In contrast to respiratory infection, diarrhoea in our study population was associated with poorer growth. The children's height increments decreased with more days of diarrhoea in a dose-response manner, but these differences only became statistically significant with the highest quartile of diarrhoea prevalence (≥2.5% days ill). The decrement in linear growth in this quartile (0.20 cm/4 months) was similar to that reported by Martorell *et al.* in a study from Guatemala[28] where a difference of 0.17 cm/4 months (or 3.5 cm/7 years) in height gain was observed between children with a high (≥5%) and a low (<5%) proportion of days with diarrhoea.

The lack of an effect of diarrhoea on weight increments in our study population might be due to the low prevalence of diarrhoea. Martorell *et al.* in their study from Guatemala reported the largest negative growth impact from diarrhoea in those children with the highest prevalence of diarrhoea. They observed that children with <5% of days of diarrhoea gained 1.5 kg more in weight over the 7-year observation period (or 71 g/4 months) than children with ≥5% of days of diarrhoea.[28] These prevalence cutoffs were far higher than the highest diarrhoea prevalence category used in our analysis.

Furthermore diarrhoea in our study population did not modify the effect of vitamin A supplementation on growth. Again the most likely explanation is that the prevalence of diarrhoea was too low being only 0.4% or on average <1 day of diarrhoea during a 4-month period. Even in the upper quartile, children only experienced 3–5 days with diarrhoea during a 4-month period. Diarrhoea might have impaired absorption of vitamin A in those children who had diarrhoea at the time of

supplementation, but the burden of diarrhoea was not sufficient to deplete vitamin A stores throughout the 4-month period. Salmonellosis, which has been reported to have a strong impact on the absorption of vitamin A,[14] was responsible for only 4% of all diarrhoea cases in the MORVITA trial. Thus, the impact of diarrhoea on the absorption and utilization of vitamin A in this population was much less than from respiratory infection.

It is reasonable to expect that any growth response to vitamin A supplementation might be mediated by its effects on morbidity.[29] However, in this study population, vitamin A supplementation had little effect on morbidity rates with no change in the incidence of diarrhoea but an 8% increase in the incidence of cough episodes.[16] Since respiratory infection did not affect growth, there is no reason to relate the small increase in incidence due to vitamin A supplementation to poor growth. Thus, in this trial, the effect of vitamin A supplementation on growth appears to be independent from its effects on morbidity.

Preschool children need 400 RE/day of vitamin A intake to permit adequate growth and other vitamin A-dependent functions, and to maintain an acceptable total body reserve of the vitamin.[24] This reserve is assumed to be enough to offset periods of low intake or increased need resulting from infections and other stresses. Thus, children meeting this normative requirement for vitamin A are less likely to have their growth impaired due to vitamin A deficiency. Conversely, children not meeting the requirement are more likely to have retarded growth if they do not receive vitamin A supplementation. However, vitamin A supplementation may not be sufficient to improve growth in children who experience frequent respiratory infections.

In summary, diarrhoea and respiratory infection have important but different roles in affecting growth and modifying the growth response to vitamin A supplementation. Our findings indicate that vitamin A supplementation resulted in a modest improvement in the linear growth of children. However, in special subgroups, such as among children with a low burden of respiratory infections and a low daily dietary intake of vitamin A, the growth benefit from vitamin A supplementation amounted to an increase of 10% of the linear growth (0.31 cm/4 months) observed in the placebo treated children. This is a sizable benefit, as the typical height increment for 1–4-year-old children in normative populations ranges from 2.3 cm/4 months to 3.8 cm/4 months (or 7 cm/year to 11.5 cm/year).[30] Finally, the linear growth response to vitamin A was diminished or removed by increasing intakes of dietary vitamin A or a heavy burden of respiratory infections especially when accompanied by fever.

Our results suggest that in populations with a high prevalence of respiratory infections, vitamin A supplementation is unlikely to improve children's growth. But in populations with relatively low prevalence of infectious disease and low vitamin A intakes, vitamin A supplementation will improve linear growth. Our findings help explain the variable growth response to vitamin A observed in earlier studies.

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