Original Article

Impact of vitamin A supplementation on health status and absenteeism of school children in Sri Lanka

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The objective of this study was to determine the impact of Vitamin A supplementation on health status and absenteeism of school children. A randomized double blind placebo controlled trial over a period of 13 months was conducted in a rural area of Sri Lanka involving 613 school children attending Grades 1-5 (aged 5 to 13 years). Children were assigned to either 200,000 IU of Vitamin A (n=297) or placebo (n=316) once every 4 months. Socio-demographic data were obtained at baseline, and anthropometry and haemoglobin concentrations were assessed at baseline and post intervention. Serum vitamin A concentrations were assayed by HPLC in a subgroup of children (n=193) before administration of each dose. School absenteeism was recorded. The two groups of children were similar at baseline in all variables. The subgroup of children was comparable to the main study population. The prevalence of vitamin A deficiency (<20 μg/dL) in the subgroup of children was 8.2%. Changes in anthropometric indices and haemoglobin concentrations were similar in the two groups. The major causes for absenteeism were non-health causes and supplemented children lost a fewer number of school days due to illness than placebo children (p=0.053). Vitamin A concentrations improved with each dose and the improvement was greater with better compliance. Vitamin A supplementation with 200,000 IU every 4 months over 13 months improved vitamin A status and school attendance but not anthropometric status of these children.

Key Words: Vitamin A supplementation, health status, school absenteeism, school children, Sri Lanka

Introduction

Health and physiological consequences attributable to vitamin A deficiency (vitamin A deficiency disorders) are a major public health problem in many developing countries affecting up to 250 million children worldwide.[1,2] Supplementation with a high dose of vitamin A is the most widely used strategy to combat vitamin A deficiency disorders.[2] Trials of vitamin A supplementation have consistently shown a beneficial effect on childhood mortality, [3-5] but the effect of vitamin A on morbidity and nutritional status is unclear. In some studies, the incidence or prevalence of infectious diseases such as diarrhoea, and respiratory infections were reduced with vitamin A supplementation.[6-9] Several studies have failed to show that vitamin A supplementation reduces morbidity. [10-12] In contrast, some studies reported that vitamin A supplementation may have a harmful effect particularly in well nourished children. Dibley *et al.* found that vitamin A supplementation increased the incidence of respiratory illness in preschool children.[13] Similarly vitamin A supplementation trials have produced mixed results in the case of child growth. There are reports indicating that vitamin A supplementation improves growth[14,15] but others have reported little or no discernable effects.[10,12,16,17]

Naluboal and Nestel attributed the conflicting results to many confounding factors such as long term recall period, differences in the age groups of children participating in the studies, and underlying vitamin A and/or overall nutritional status of the children which influence the response to vitamin A supplementation and emphasise further evaluation of vitamin A supplementation in different settings.[18]

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Up to date most of the studies have been carried out among preschool children or infants. The effect of vitamin A supplementation on school children has not been adequately investigated. Children need to attend school regularly to take full advantage of opportunities provided by the schools. Studies have shown that children lose a considerable amount of school days as a consequence of diseases, [19,20] which could have been prevented. A previous study of children of similar age in this area reported that malaria is the main cause of school absenteeism. Malaria chemoprophylaxis improved school attendance significantly. The prevalence of protein energy malnutrition was also high with 30% underweight, 15% wasted and 14% stunted. Over 60% of the children were anaemic but the prevalence of geo-helminth infections was low (ranged from 2% to 5.42%).[20] The national vitamin A survey conducted in 1995/1996 reported that 35 % of children 6 to 71 months of age resident in the Moneragala district had a vitamin A concentration <20 μg/ dL. [42] We report the impact of vitamin A supplementation on health status and absenteeism of school children attending two schools in a rural area of Sri Lanka.

Materials and Methods

A randomised double blind placebo controlled trial of vitamin A supplementation over a period of 13 months commencing June 2001 was conducted among children attending Grades 1-5 (age 5-13 years) at two schools in the Kataragama area of the Moneragala District in southern Sri Lanka. Being a rural area, paddy cultivation is the primary occupation of the residents.

Enrolment of children

Children in Grades 1-5 of two schools were recruited into the study. Children with a history of epilepsy, known hypersensitivity or diagnosed as having a chronic disease such as cardiac or renal disorder were excluded from the study. Written informed consent was obtained from the parents/guardians of the children and class teachers before enrolment. The trial was approved by the Ethical Review Committee of the Faculty of Medicine, University of Colombo, Sri Lanka. Permission to conduct the study was obtained from the Zonal Education Director, Wellawaya and the Provincial Health Authority, Uva province.

Baseline studies

Baseline studies were carried out during the 1st week of June, 2001. Parents were instructed to be present at the school on the day of the survey of the respective class. A detailed socio-demographic profile of children and their families were obtained from parents/guardians at enrolment of children using an interviewer-administered questionnaire. A finger prick blood sample was obtained for estimation of haemoglobin concentration using the Hemocue method and blood smear examination for malarial parasites. Blood smears were prepared following WHO guidelines and malaria diagnosis was done on microscopy.[21] The heights and the weights of the children were measured according to WHO guidelines.[22]

Intervention trial

Children in each class were randomly assigned to either Vitamin A or placebo arms using computer generated random numbers. A total of 659 children were included in the study. Of them, 322 were assigned to the Vitamin A arm while the rest were assigned to the placebo arm.

A labelled plastic container with five capsules of Vitamin A or placebo (containing 400 gms of Lactose) depending on the treatment arm was assigned for a child. Each child was administered a capsule (200 000 IU of Vitamin A or placebo) every 4 months. Drugs were administered to the children by the investigators with the assistance of class teachers. After the administration of drugs, children were observed by the class teachers and the investigators. If the child vomited the capsule within one hour of intake the dose was repeated. Any symptoms such as headache, abdominal pain etc. reported by the children was recorded. The investigators visited the schools for a week (5 consecutive school days) in order to administer the dose to children who were absent on previous visits. The first dose was given in the 1st week of June 2001. The second and third doses were given in November 2001 and March 2002 respectively.

During the period of intervention the patients were informed to send a letter of excuse indicating the reason for being absent whenever the child was absent. Each day the class teacher recorded the reason for being absent for each child while marking the attendance register. Any illness episode requiring a hospital visit was cross checked with hospital records.

Post intervention studies

A post intervention survey was carried out 13 months after supplementation during the last week of June 2002. Heights and weights of the children were measured and haemoglobin concentrations were assessed as in the baseline survey.

Specimen collections and analysis of serum Vitamin A

Two ml venous blood were collected from a selected subsample of children enrolled in one class of all grades i.e., classes 1A, 2A, 3A, 4A and 5A, before administering each dose i.e., at baseline, before administering the 2nd (4th month) and 3rd (8th month) doses of vitamin A or placebo using disposable syringes under aseptic conditions. Serum was separated and stored at -80^{0}C until biochemical analysis. Serum vitamin A concentrations were assayed by reversed-phase HPLC according to the method of Bieri *et al.*[23] A total of 200μL of serum was added to 100 μL of a standard solution of retinyl acetate and 100 μL 95% ethanol, and serum vitamin A was extracted with 600 μL hexane. A 400μL portion of the hexane extract was evaporated to dryness under a stream of nitrogen gas, re-dissolved in 100 μL mobile phase, and an aliquot of 20 μL of the solution was injected into a C_{18}, reversed phase 150 mm × 4.6 mm HPLC column (Wartex©, UK). The mobile phase (methanol:water - 95:5 volume) was delivered at a flow rate of 1 mL/min. Vitamin A (eluting time 4 min) was detected at 325 nm in a Beakman ultraviolet detector. Serum vitamin A concentrations were calculated from the standard curve after correction of percent loss using the internal standard. Serum Vitamin A concentrations were reported in μg/dL.

Statistical analyses
Weight-for-age (WAZ), weight-for-height (WHZ) and height-for-age (HAZ) were expressed in terms of Z-scores as a deviation of the median of the growth reference curves of the National Center for Health Statistics using EPIINFO. All values flagged by the programme after re-checking were not considered in the analysis. House types were classified as "good" or "poor" based on the material used for construction of walls and roof. Houses having complete plastered walls and roofs with tiles/asbestos or tin sheets were classified as "good" houses. The others were considered as "poor" houses. Differences in outcome variables between vitamin A and placebo groups were compared by using independent sample t-tests and ANOVA. Changes in the variables at different time points during the trial were compared using the paired t-test.

Results
A total of 659 children comprising 322 children who received vitamin A and 337 who received the placebo were recruited into the study. Of the 659 children, 46 (7.0%) did not complete the trial due to leaving school (n=42), moving residence (n=2) and dropping out of school (n=2). There was no significant difference in the drop out rates between vitamin A (7.8%) and placebo (6.2%) groups (p=0.440). Serum vitamin A concentrations were assayed in a subgroup of children which included 193 children (n=92 in vitamin A group and n=101 in placebo groups). The sociodemographic profiles ofchildren who received vitamin A and placebo in both the study population and the subgroup of children whose vitamin A concentrations were assayed were comparable (Table 1).

Effect of intervention
The haemoglobin concentrations in both vitamin A and placebo groups improved during the trial (p=0.021 and p=0.001 respectively) but the difference in improvement was not statistically significant (Table 2). Weight-for-age Z scores post intervention were better in both groups of children as compared to baseline values but the difference was significant only in children receiving vitamin A. There were significant increases in weight-for-height and decreases in height-for-age in both groups of children post intervention as compared to baseline values. The differences in the improvement of weight-for-height and the decrease of height-for-age between the 2 groups of children were not significant.

Causes for school absenteeism during the intervention
Table 3 gives the causes for school absenteeism during the intervention. Non-health related reasons such as staying at home to help their parents with work in the fields and at home, no food, heavy rain etc., were the main reasons for absenteeism during the intervention. There were no significant differences in absenteeism due to non-health related reasons between children who received vitamin A or placebo as expected. Cough and cold was the commonest illness among the children. Children who received vitamin A lost a fewer number of school days due to cough and cold as compared to those of the

Table 1 Sociodemographic profile of study population and subgroup of children whose vitamin A concentrations were assayed

Variable	Study population				Subgroup of children			
	Vitamin A (n=297)		Placebo (n=316)		Vitamin A (n=92)		Placebo (n=101)	
Sex	n	%	n	%	n	%	n	%
Male	148	49.8	168	53.2	41	44.6	50	49.5
Female	149	50.2	148	46.8	51	55.4	51	50.5
Age at recruitment (years)								
6-9	209	70.4	216	68.4	65	70.7	68	67.3
9.1-12	79	26.6	93	29.4	26	28.3	31	30.7
>12	9	3.0	7	2.2	1	1.1	2	2.0
Mother's education								
None	11	3.7	12	3.8	3	3.3	2	2.0
Grade 1-5	109	36.7	94	29.7	35	38.0	30	29.7
Grade 6-10	158	53.2	183	57.9	47	51.5	63	62.4
>Grade 10	19	6.4	27	8.5	7	7.6	6	5.9
Father's education								
None	12	4.0	9	2.8	12	4.0	9	2.8
Grade 1-5	131	44.1	132	41.8	131	44.1	132	41.8
Grade 6-10	141	47.5	161	50.9	141	47.5	161	50.8
>Grade 10	13	4.4	14	4.4	13	4.4	14	4.4
Monthly family income (SL Rs)								
<1000	109	36.7	106	33.5	30	32.6	32	31.7
1000-3000	173	58.2	181	57.3	60	65.2	62	61.4
>3000	15	5.1	29	9.2	2	2.2	7	6.9
House type*								
Good	65	21.9	76	24.9	16	17.4	20	19.8
Poor	232	78.1	240	75.9	76	82.6	81	80.2
Total	297	100.1	316	100.0	92	100.0	101	100.0

* Houses having complete plastered walls and roofs made of tiles/asbestos or tin sheets were classified as good houses. The rest were classified as poor houses.

Table 2 Effect of intervention on haemoglobin concentration and anthropometric indices

Variable	Vitamin A			Placebo			*p*-value
	n	mean	SD	n	mean	SD	
Haemoglobin concentration (g/dL) $^{\alpha}$							
Baseline	193	12.1	1.5	216	11.9	1.4	
Post intervention	193	12.4	1.1	216	12.6	1.1	
Difference$^{\gamma}$	193	0.3	1.6	216	0.4	1.7	0.480
p-value$^{\#}$	0.021			0.001			
weight-for-height (z-score) $^{\beta}$							
Baseline	172	-1.49	0.84	175	-1.44	0.78	
Post intervention	172	-1.28	0.86	175	-1.27	0.83	
Difference$^{\gamma}$	172	0.21	0.39	175	0.17	0.38	0.407
p-value$^{\#}$	<0.001			<0.001			
Height-for-age (z-score) $^{\beta}$							
Baseline	221	-1.21	0.96	245	-1.13	1.13	
Post intervention	221	-1.38	0.92	245	-1.31	1.10	
Difference$^{\gamma}$	221	-0.17	0.31	245	-0.18	0.3	0.437
p-value$^{\#}$	<0.001			<0.001			

$^{\alpha}$ only children who had both baseline and post intervention blood samples were included
$^{\beta}$ only children who were not flagged by EPIINFO at both measurements were included
* *p*-value comparing vitamin A and placebo groups of children based on independent sample t-test
$^{\#}$ *p*-value comparing baseline and post intervention measurements based on paired t-test
$^{\gamma}$ Difference between post intervention and baseline values

Table 3 Causes for school absenteeism during the intervention

Cause	Absenteeism (days) of children who received				*p*-value*
	Vitamin A (n=297)		Placebo (n=316)		
	mean	SD	mean	SD	
Headache	0.2	0.5	0.3	0.7	0.066
Cough and cold	5.8	5.6	6.7	6.5	0.053
Stomach ache	0.7	1.5	0.8	1.6	0.844
Other illness	1.6	3.3	1.6	3.8	0.764
Non health causes	21.2	15.5	20.1	14.4	0.345
All causes	29.5	18.6	29.5	17.9	0.994

* *p*-value based on independent samples t-test

placebo group (5.8 vs 6.7 school days, respectively) (*p*=0.053). There were no significant differences in the average number of school days lost due to headache or stomach ache between the two groups of children.

Serum vitamin A concentrations

Changes in serum vitamin A concentrations of the sub-group of children during the 8-month period are given in Table 4. At baseline, serum vitamin A concentrations were higher in children who received placebo but the difference was not statistically significant. At four months, children who received vitamin A had a significantly higher serum vitamin A concentration as compared to their baseline value in contrast to children of the placebo group who had a lower concentration than their baseline value. Similarly, at 8 months, children given vitamin A had higher values than at baseline (*p*<0.001) or at 4 months (*p*=0.068) but the opposite was seen in placebo children. The differences in vitamin A concentrations

Table 4 Serum vitamin A concentrations in subgroup of children during the study

Time point	Serum vitamin A concentration (µg/dL) of children who received						*p*-value*
	Vitamin A			Placebo			
	n	mean	SD	n	mean	SD	
Baseline	87	34.5	11.7	95	36.4	12.6	0.257
4th month	88	38.9	16.2	99	34.4	13.7	0.044
Difference (4th month-baseline)	86	4.5	17.6	95	-2.2	17.5	0.010
p-value[1]	0.018			0.218			
8th month	92	42.3	17.0	100	33.4	13.6	<0.001
Difference (8th month-4th month)	88	3.6	18.2	99	-0.9	18.1	0.095
p-value[2]	0.068			0.699			
Difference (8th month-baseline)	87	8.2	18.4	95	-2.8	16.4	<0.001
p-value[3]	<0.001			0.118			

* p-value based on independent sample t-test
[1] Comparison of vitamin A concentration between 4th month and baseline using the paired t-test
[2] Comparison of vitamin A concentration between 8th month and 4th month using the paired t-test
[3] Comparison of vitamin A concentration between 8th month and baseline using the paired t-test

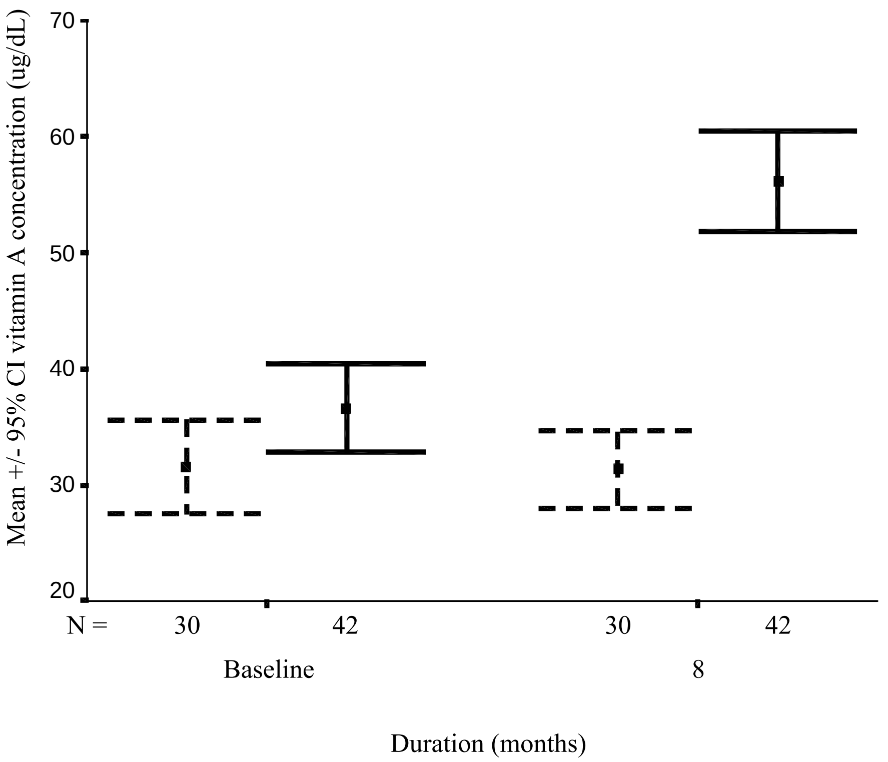

Figure 1. Change in serum vitamin A concentration of the subgroup of children by compliance during the first 8 months. (-- ▌ --), Children who received 1 capsule; (▌) children who received 2 capsules.

between the 2 groups of children were significant at 4 months (p=0.044) and at 8 months (p<0.001) (Table 4). There was no significant decline in vitamin A concentrations in children who received placebo at the 8th month as compared to their baseline values.

Compliance to vitamin A supplementation

All children in the vitamin A arm of the trial received at least one dose of vitamin A during the intervention. Twenty five children (8.4%) received one dose, 75 (25.3%) received two doses and 197 (66.3%) children received all three doses.

At 8 months, during measurement of vitamin A concentrations before administration of treatment, children may have received 1 or 2 doses, and these 2 groups of children were compared. There was no significant difference in baseline vitamin A concentrations between children who received one and two doses. At the 8th month, vitamin A concentrations of children who received two doses were higher than that of the children who received only one dose (p<0.001) and the difference between 8th month and baseline concentrations between the two groups of children was significant (p<0.001). The increase in vitamin A concentrations at 8 months as compared to baseline values in children who received 2 doses was significant. There was no significant difference between vitamin A concentrations at 8 months and baseline in children who received 1 capsule (Fig 1).

Discussion

This trial was carried out to determine the impact of vitamin A supplementation on the health status and school absenteeism of children 5-13 years of age in rural Sri Lanka attending grades 1-5. Health status of the children was assessed by anthropometry, haemoglobin concentrations and health reasons for school absenteeism. Vitamin A supplementation with 200,000 IU of retinol once in four months over a period of eight months decreased school absenteeism due to cough and cold over a 13 month period. Supplementation improved serum vitamin A concentrations and sustained it for at least for 4 months. As expected, serum vitamin A concentrations correlated with compliance.

Though a significant improvement in the anthropometric indices was observed at the end of the study, irrespective of the treatment, the improvements in children receiving vitamin A were higher than those of placebo group, but the differences were not statistically significant. Although vitamin A is known to play a role in cell differentiation and organ growth[24] and vitamin A deficiency has been shown to impair growth in animal models,[25] randomized intervention trials have yielded conflicting results. It has been hypothesized that vitamin A supplementation is unlikely to improve the growth of children who are only mildly to moderately malnourished and it could exert a positive effect only on growth of severely vitamin A deficient children.[26] West *et al.* also reported that the growth impact of vitamin A is more evident among xerophthalmic children than non-xerophthalmic children.[27] Improved weight gain[14] and linear growth[15] have been reported in vitamin A supplemented children in populations that were, in general, in better health and better nourished. These studies were carried out among young children. There can be age specific effects of vitamin A supplementation on growth.[28] This population could be classified as having mild vitamin A deficiency as the prevalence of vitamin A deficiency was only 8.2% at baseline (serum vitamin A concentrations less than 20 µg/dL). This and the fact that children in this study being 5-13 years of age may explain the reasons for the lack of evidence of growth promotion in children supplemented with vitamin A.

Vitamin A is known to play a role in improving haemoglobin status, but the biological mechanisms by which vitamin A influences haemoglobin status are not well understood. Vitamin A is needed for erythropoiesis,[29] and haemoglobin is not incorporated into red blood cells in a normal way in persons with vitamin A deficiency.[30] Vitamin A is reported to enhance iron absorption.[31,32] Controlled trials in Guatemala[33] and Indonesia[15, 34] have reported that vitamin A supplementation increases haemoglobin in preschool children. Walczyk *et al*. have reported that vitamin A influences haemoglobin status only in subjects with impaired vitamin A status.[30] In this study, haemoglobin concentrations of children of both groups improved significantly at the end of the trial but there was no significant difference between the improvements of haemoglobin concentrations in the two groups of children. The lack of a significant difference in the haemoglobin concentration between the two groups of children, as reported in other studies, may be due to age, nutritional status, and prevalences of geo-helminth infection and vitamin A deficiency differences.

The major cause for school absenteeism was non-health related causes. In an earlier study in this population, the major cause of school absenteeism was acquisition of malaria. Non-health related causes were the next important one followed by other diseases.[20] With low transmission of malaria during the study period, non-health related causes dominated reasons for school absenteeism. There was no significant difference in school absenteeism due to health and non-health related causes between children of placebo and treatment groups. Most of the non-health related causes were helping with household work and in the fields, and inadequate facilities to attend school (unavailability of clean uniform etc.) [20]. The cause of absenteeism was assessed using the letters sent by the parents to the class teachers. Even though it is likely that children may attend school with a cough and cold, the very fact that absenteeism was less may suggest a milder form of the disease. Though the caretakers were made aware of the importance of proper reporting of absenteeism, there still may be some misclassification.

The effects of vitamin A supplementation on infections are contradictory.[18] Together with expected variations under different study settings such as age and sex differences, errors in definition of infections[13], data collection on a limited number of symptoms / conditions [10,11] and long recall periods in some studies[35,36] have been attributed to conflicting results. In this study, the reason for absenteeism was recorded on the very first day that the child attended the school after being absent by the class teacher using the letter of excuse sent by the parents. Therefore, errors due to long recall periods are unlikely. The type of the disease which absented the child was reported as perceived by the parents. Health reasons for absenteeism depends on the existing disease spectrum prevalent in an area. Hence, vitamin A supplementation would have been more beneficial had children experienced more infections during the study period. Recent community based studies have reported a decrease in the incidence and duration of diseases by vitamin A supplementation.[37-39]

The Kataragama area of Sri Lanka is situated in the dry zone of the country. The dry zone of the country is endemic for malaria with unstable transmission. Both *P.vivax* and *P.falciparum* malaria are prevalent in the area. In the past, malaria was highly endemic in the area.[40] During the study period, malaria transmission was low in the area as in the rest of the country and only one and two malaria cases were reported among children receiving placebo and vitamin A respectively. If the incidence of malaria was high, and if vitamin A did in fact have an effect on morbidity, then the impact of vitamin A supplementation on school absenteeism would have been much greater.

The major cause for school absenteeism in this group of children was non-health related causes such as helping their parents in agricultural activities. In the past, in this same population, the major cause for school absenteeism was malaria.[20] It is also possible that the growth promotion action of vitamin A is an indirect one based on its effect on morbidity. Thus the beneficial effects of vitamin A on growth are likely to be more pronounced in areas where infections are common.

Improvement in serum vitamin A concentrations is an important outcome indicator in evaluation of vitamin A intervention programmes.[43] It is clearly seen in this study that serum vitamin A concentrations of children improve with regular administration of vitamin A doses, the improvement being better with better compliance. During the first eight months of follow up, children who received two doses of vitamin A had a significantly higher serum vitamin A concentration than those who received one dose. The improvement in serum vitamin A concentrations during the first four months was more marked than in the later four months period. The decrease in the improvement of vitamin A concentrations in supplemented children between the 4^{th} and the 8^{th} month may be due decreased uptake as a result of replenishment of vitamin A reserves. Serum vitamin A concentrations of children in the placebo group were similar at successive measurements and rules out any seasonal variations in vitamin A concentrations in this population during the follow up period.

The subgroup of children whose vitamin A concentrations were assayed represented all age groups and was socio-demographically comparable to the main study population. Hence the results of the subgroup could be generalized to the larger study group and the reduction in morbidity could be attributed directly to improvement in serum vitamin A concentrations. The relatively low prevalence of vitamin A deficiency and infections in the community and differences in the age groups studied may explain the lack of evidence of the effects of vitamin A supplementation reported in other studies. Nevertheless, a clear improvement of vitamin A status was observed with supplementation of these 5-13 year old school children.

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Original Article

Impact of vitamin A supplementation on health status and absenteeism of school children in Sri Lanka

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維生素 A 的補充對於斯里蘭卡學童的健康狀況及曠課的影響

本研究的目的為評估維生素 A 的補充對學童的健康狀況及曠課的影響。本研究為一個為期 13 個月的隨機雙盲安慰劑控制試驗，對象為 613 名斯里蘭卡鄉下 1-5 年級的學童(年齡 5-13 歲)。將兒童分派為補充維生素 A 200,000 IU (n=297)或是安慰劑組(n=316)，每四個月一次。社會人口學變項在研究之初收集，體位資料及血紅素濃度在研究之初及介入後評估。採用 HPLC 分析子群的學童(n=193) 每一次劑量施予之前的血清維生素 A 濃度。紀錄學校曠課的情形。兩組學童在研究之初的所有變項均類似。子群學童與主要研究族群可以類比。子群的維生素 A 缺乏(<20 μg/dL)盛行率為 8.2%。兩組學童的體位測量指標及血紅素濃度的改變量相似。曠課的主要原因為非健康因素，補充學童因為疾病曠課的天數較安慰劑組的學童少($p=0.053$)。維生素 A 濃度隨著每一個劑量而改善，而順從度較好者改善愈多。為期 13 個月的每四個月補充維生素 A 200,000 IU 改善維生素 A 營養狀況及學校出席狀況，但對體位沒有影響。

關鍵字：維生素 A 補充、健康狀況、學校曠課、學童、斯里蘭卡。