Original Article

Effect of vitamin A on severity of acute diarrhea in children

Marlisye Marpaung, Supriatmo, Atan Baas Sinuhaji

Abstract

Background Vitamin A deficiency may increase the risk or be a cause of diarrhea. Many studies have been conducted on the efficacy of vitamin A in the management of acute diarrhea, but the outcomes remain inconclusive.

Objective To determine the effectiveness of vitamin A in reducing the severity of acute diarrhea in children.

Methods We performed a single-blind-randomized controlled trial in the Secanggang District, Langkat Regency, North of Sumatera, from August 2009 to January 2010 in children aged 6 months to 5 years, who had diarrheas. Subjects were divided into two groups. Group 1 received a single dose of vitamin A (100,000 IU for subjects aged 6 to 11 month old or with body weights ≤ 10 kg, or 200,000 IU for subjects aged ≥ 12 month old or with body weights > 10 kg). Group 2 received a single dose of placebo. The establishment of severity was based on changes in diarrheal frequency, stool consistency, volume and duration of diarrhea after treatment. We performed independent T-test and Chi square tests for statistical analyses. The study was an intention-to-treat analysis.

Results We enrolled 120 children who were randomized into two groups of 60 subjects each. Group 1, received vitamin A and group 2 received a placebo. The results showed significant differences between the two groups in stool volume starting on the first day (95%CI 192.30 to 3237.51; P=0.001), as well as diarrheal frequency (P=0.001) and stool consistency (P=0.001) on the second day observation and duration of diarrhea following treatment (95%CI - 40.60 to - 25.79; P=0.001;).

Conclusions Vitamin A supplementation is effective in reducing the severity of acute diarrhea in children under five years of age. [Paediatr Indones. 2013;53:125-31.]

Keywords: *acute diarrhea, vitamin A, severity of acute diarrhea*

In Indonesia, diarrhea remains a major cause of death in infants and children. During the 1980s and 1990s, researchers began to question whether deficiencies in specific micronutrients might affect the risk for diarrhea.[1] In the gastrointestinal tract, vitamin A deficiency (VAD) is both a cause and a consequence of diarrheal disease.[2] At the beginning of the 20th century, vitamin A was commonly known as the anti-infective vitamin, when its deficiency was shown to be associated with various infections.[3,4] However, the mechanism by which vitamin A protects the body against infection is unclear.[5] A 1968 Swiss study reported that "no nutrient deficiency is more consistently synergistic with infectious disease than that of vitamin A.[6] Green HN *et al*[5] and Grotto I *et al*[7] suggest, on the basis of animal studies, that vitamin A has anti-infective activity.

Many studies have been conducted on the effect of vitamin A on acute diarrheal management, but

the outcomes remain inconclusive. In Indonesia, clinical trials on the impact of vitamin A on diarrheal prevalence[8] and on the duration of diarrhea[9] were undertaken but neither clearly showed the usefulness of vitamin A on reducing prevalence or duration of diarrhea. There has been no Indonesian studies on the impact of vitamin A on diarrheal severity. So we aimed to determine the effectiveness of vitamin A in reducing the severity of acute diarrhea.

Methods

We conducted a single-blind, randomized controlled trial in the Secanggang District, Langkat Regency, North Sumatera, from August 2009 to January 2010. We included children aged 6 months to 5 years with acute diarrhea. We exclude children with severe dehydration, cholera, critically ill conditions (severe malnutrition, encephalitis, meningitis, sepsis, bronchopneumonia, and tuberculosis) due to their need for therapy that might influence the study. We also excluded subjects who had consumed vitamin A in the prior 4 months to avoid hypervitaminosis conditions, or suffered from measles in the 6 weeks prior the study, conditions that may lead to vitamin A deficiency and have a positive response to vitamin A supplementation. An informed consent was obtained from all parents and the study was approved by the Research Ethics Commitee of the University of North Sumatera Medical School.

Subjects recruitment was centered at the Puskesmas Hinai Kiri, a local government clinic in the Secanggang District. Every three days subjects were recruited by consecutive sampling method. On admission, standard history was taken, a thorough physical examination was performed by a physician and parents were asked to fill questionnaires. Dehydration was assessed and treated according to the WHO 2005 guidelines using oral or parenteral rehydration solution.

Subjects were randomized into two groups by a random number table method. We gave a single dose of vitamin A to group 1, with doses of 100.000 IU for subjects aged 6 - 11 months or with body weights ≤ 10 kg, or 200.000 IU for subjects aged ≥ 12 months or with body weights > 10 kg. A single dose of placebo was given to children in group 2. Both suplements were

given at the time of enrollment. Subjects with mild-moderate dehydration were rehydrated prior to vitamin A or placebo given. Parents were asked to monitor their child's diarrheal frequency, stool consistency and stool volume at every diarrheal episode. Diarrhea monitoring charts were given to parents and as well as explanation of how to fill the chart correctly.

All subjects were monitored (either at the local government clinic or by a home visit) every 3 days until recovery. Recovery from diarrhea was defined as a frequency of defecation less than 3 times a day, loose or soft stool consistency becoming normal, and stool volume becoming normal (less than 200 mL per day)[10] during 48 hours.[11] Acute diarrheal illness usually resolves spontaneously within 7-10 days without treatment,[12] but a new episode of diarrhea can occur after two full days without treatment.[11]

At every visit we assessed the monitoring chart and obtained information on any complications (vomiting, nausea, fever, headache, or seizure) and any medication given to subjects, in addition to the vitamin A/placebo. Monitoring for the recovery from acute diarrhea was done daily and was based on changes of frequency, stool consistency and volume, as well as duration of diarrhea.

We used *SPSS version 15.0* and *Microsoft Excel 2007* for data processing. Independent T-test was used to evaluate the relationship between vitamin A (nominal scale) and diarrheal frequency, diarrheal duration and stool volume (numeric scale). Chi square-test was used to evaluate the relationship between vitamin A (nominal scale) and stool consistency (ordinal scale). This study was an intention-to-treat analysis. Differences were considered significant if P values were < 0.05 with a 95% CI.

Results

One-hundred twenty-nine children with diarrhea were recruited into the study. Nine children were excluded (5 children with severe malnutrition, 2 with severe dehydration, and 2 parents refused to participate). The remaining 120 children were randomized into two groups: 60 children received vitamin A and the rest received a placebo (**Figure 1**).

Subjects' baseline characteristics were similar

in both groups. We included subjects who meet the diarrhea characteristics. Subjects were children aged 6 to 60 months with a mean age of 24.1 (SD 12.39) months.

The mean diarrheal frequency, stool consistency, stool volume and duration of diarrhea for all subjects were 5.1 (SD 1.6) times in 24 hours, liquid consistency 75.7 (SD 26.93) mL per-episode and 26.1 (SD 14.85) hours, respectively. Most subjects were not dehydrated (69%), while mild-moderate dehydration was found in 31% subjects. Subjects' characteristics on both groups were similar as shown in **Table 1**.

Diarrheal severity in subjects of both groups was assessed daily for 5 days. **Figure 2** shows significant differencess in mean daily diarrheal frequency after therapy between the vitamin A group and placebo group from the second to fifth days of assessment.

In the vitamin A group, the stool consistency recovered sooner than those in placebo group, as shown in **Table 2**.

We also found that children in vitamin A group excreted less fecal volume compared to those in placebo group since the first day after treatment (**Figure 3**).

Duration of diarrhea in the vitamin A group was shorter than that of the placebo group (95%CI -40.60 to -25.79; P=0.001), with the mean durations of diarrhea of 84.0 (SD 19.51) hours and 117.2 (SD 21.68) hours, respectively. In addition, we also found a significant difference in the duration of diarrhea

from the first day of diarrhea until recovery in the two groups (95%CI -49.70 to -29.46; P=0.001), with, faster recovery in the vitamin A group compared to the placebo group; 106.9 (SD 27.73) hours vs 146.5 (SD 32.30) hours (**Table 3**).

Discussion

In this study, we found that the administration of vitamin A resulted in lower diarrhea frequency, better stool consistency and shorter duration of diarrhea. In the vitamin A group, diarrheal frequency and stool consistency became normal starting from the second day and stool volume was normal from the first day of assessment. In contrast, in the placebo group diarrheal frequency and stool volume became normal starting from the third day while stool consistency was recovered starting on the fourth day of assessment. These results support previous findings about lower concentration of vitamin A in children with diarrhea that its supplementation may reduce the risk of diarrhea.[13]

Diarrhea disease may cause VAD by several mechanisms. First, steatorrhea can lead to a generalized loss of fat-soluble vitamins. Second, damage to the brush border may inhibit the function of brush border retinyl esterases, which contributes to the intestinal absorption of vitamin A. Conversely, VAD may predispose a child to diarrhea in a number of ways. Vitamin
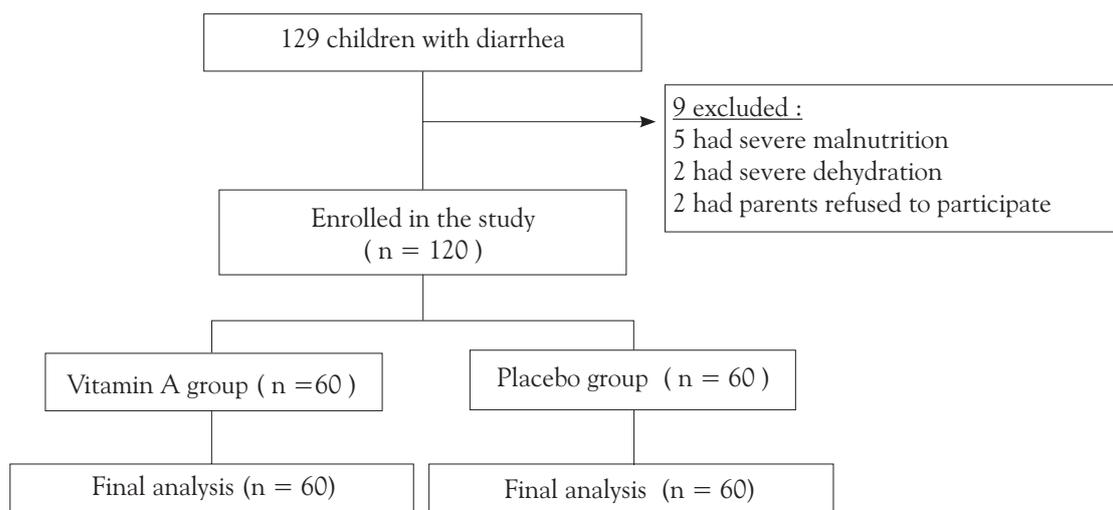
Figure 1. Study flow chart

Table 1. Baseline characteristics of subjects

Characteristics	Vitamin A group (n=60)	Placebo group (n=60)
Mean age (SD), months	21.9 (13.48)	26.2 (10.91)
Sex, n (%)		
Male	32 (53.3)	30 (50.0)
Female	28 (46.7)	30 (50.0)
Mean BW/BH* (SD)	95.2 (1.67)	97.2 (2.03)
Mean diarrheal frequency (SD), times/day	5.1 (1.86)	5.1 (1.32)
Stool consistency, n (%)		
Liquid	4 (90.0)	52 (86.7)
Soft	6 (10.0)	8 (13.3)
Mean stool volume (SD), mL/episode	73.5 (28.92)	78.0 (24.82)
Mean diarrheal duration (SD), hours	22.9 (12.74)	29.3 (16.18)
Dehydration status, n (%)		
No dehydration	41 (68.3)	42 (70.0)
Mild-moderate	19 (31.7)	18 (30.0)

*BW: body weight; BH: body height

Table 2. Stool consistency of subjects following treatment

Stool consistency	Vitamin A group n = 60				Placebo group n = 60				P value
	Def. (-)* n (%)	liquid n (%)	soft n (%)	normal n (%)	Def.* (-) n (%)	liquid n (%)	soft n (%)	normal n (%)	
Day I	0	45 (75.0)	14 (23.3)	1 (1.6)	0	52 (86.7)	8 (13.3)	0	0.117
Day II	1 (1.7)	16 (26.6)	36 (60.0)	7 (11.7)	0	46 (76.6)	14 (23.4)	0	0.001
Day III	8 (13.4)	0	20 (33.3)	32 (53.3)	1 (1.6)	17 (28.4)	42 (70.0)	0	0.001
Day IV	27 (45.0)	0	5 (8.3)	28 (46.6)	4 (6.7)	1 (1.6)	50 (83.3)	5 (8.3)	0.007
Day V	41 (68.3)	0	0	19 (31.7)	26 (43.3)	0	19 (31.7)	15 (25.0)	0.001

*Def. (-) = no defecation

Table 3. Mean duration of diarrhea

Duration of diarrhea (hour)	Vitamin A mean (SD)	Placebo mean (SD)	95% CI of difference	P value
Duratiion between treatment until recovered	84.0 (19.51)	117.2 (21.68)	- 40.60; - 25.79	0.001
Duration between initial symptoms of diarrhea until recovered	106.9 (27.73)	146.5 (32.30)	- 49.70; - 29.46	0.001

Note : a : 95%CI = - 0.74 ; 0.14 ; P = 0.184
b : 95%CI = - 1.34 ; - 0.65 ; P = 0.001
c : 95%CI = - 1.69 ; - 1.10 ; P = 0.001
d : 95%CI = - 1.34 ; - 0.75 ; P = 0.001
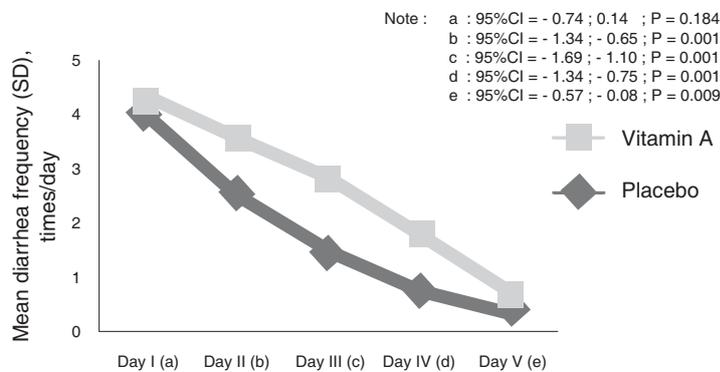e : 95%CI = - 0.57 ; - 0.08 ; P = 0.009

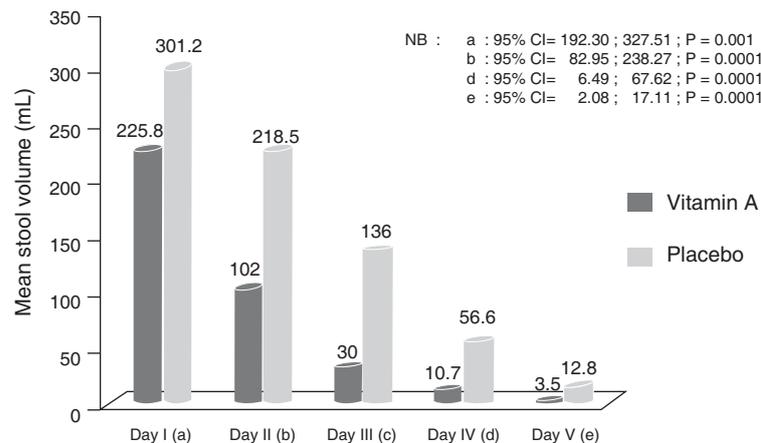**Figure 2**. Daily diarrheal frequency of subjects following treatment

Figure 3. Daily stool volume of subjects following treatment

A deficiency adversely affects the epithelial lining, leading to decreased mucous secretion and weakened local barriers to infection. Vitamin A deficiency may also lead to goblet cell depletion, abnormal villous architecture and villous atrophy, as well as adversely affecting humoral and cellular immune functions.[2,14] Thus, the International Vitamin A Consultative Group (IVACG) released the *Policy Statement on Vitamin A, Diarrhea, and Measles* in 1996, recommending vitamin A supplementation as an important strategy to reduce the consequences of VAD.[15]

The relationship between acute diarrhea and vitamin A status was examined in 137 children in Lima, Peru, by measuring the retinol concentrations in serum specimens of 72 children with diarrhea and 65 illness-free control children. Salazar-Lindo E *et al.* showed that serum retinol concentration was significantly lower in children with diarrhea than in those without diarrhea.[16] A Malatya, Turkey study also demonstrated that serum vitamin A was lower in children with recurrent diarrhea.[17] Nevertheless, a hospital-based study showed that vitamin A supplementation could reduce the risk of diarrhea.[13] A study in Bangladesh found that decreased intestinal absorption of vitamin A was associated with various infections, especially diarrhea, helminthiasis and respiratory infections. Their findings suggested a strong association between diarrhea and VAD in children, although it was not clear whether diarrhea precipitated VAD or VAD predisposed the aptinets to diarrhea or other infections.[18] Other studies also found an association of prolonged and dysenteric diarrhea with VAD.[19-20]

A study suggested that gastrointestinal integrity is severely impaired during illness, but responsive to the additional of vitamin A.[3] Another study measured the gut integrity in infants whose suffered from diarrhea or respiratory diseases, and found that the vitamin A group had more rapid improvement in gut integrity than the placebo group, although the mechanism was not clear.[21]

An estimated 254 million preschool childen in the world are at risk of VAD, with 50% of these children from Southeast Asia.[22] With regard to the high VAD prevalence and its side effects during childhood, the WHO recommends that vitamin A supplementation be given to all children especially those in areas where VAD and xeropthalmia are known to constitute a significant public health problem.[23] The currently recommended doses are 100 000 IU at age 6-11 months and 200 000 IU at age $\geq$ 12 months every 3-6 months.[23]

Our study was conducted in Indonesian's village. The total number of inhabitants was 69.940 people, of which 29.406 (42.04%) were children. Subjects were given vitamin A in accordance with WHO recommended doses, shown to be effective for reducing mortality and morbidity caused by VAD and with few side effects.[24] Furthermore, subjects with clinical vitamin A deficiency of "rabun senja" or side effects due to vitamin A supplementation were not found.

Studies conducted in many countries have shown a benefit of vitamin A in treating diarrhea.[25] Several meta-analyses were conducted during the 1990s which showed that vitamin A supplementation decreased diarrheal mortality and reduced diarrheal severity.[7] A clinical trial in Brazil showed that the severity of diarrheal disease was reduced by vitamin A supplementation.[25] In addition, a double-blind, placebo-controlled trial in a Calcutta community of children aged 12 to 71 months who received either vitamin A 200.000 IU or placebo, showed that there was a significant reduction in the average duration of diarrhea per episode.[26] In New Delhi, a randomized, controlled trial was conducted in children with diarrhea aged 6 months to 5 years with diarrhea duration of < 72 hours. Subjects received either single dose of vitamin A, according to WHO recommendations, or a placebo. There was no significant difference in the mean duration of diarrhea between the two groups. However, in children with pre-existing VAD, a beneficial effect of vitamin A was noticed.[27] Another double-blind, controlled study in New Delhi, examined the effect of 200.000 IU of vitamin A on acute diarrhea in children aged 1 to 5 years, and concluded that vitamin A may reduce the severity of diarrhea.[28]

Based on observation of diarrheal frequency, stool consistency and volume after therapy, we found that the vitamin A group had significantly shorter duration to recovery following treatment compared to that of the placebo group, 84.0 hours vs 117.2 hours, respectively. Furthermore, the mean diarrhea starting from the first day of symptoms until recovery was also significantly shorter in the vitamin A group (106.9 hours) than in the placebo group (146.5 hours).

Results from two previous Indonesian studies showed no effect of vitamin A supplementation on diarrhea in children. In Aceh, a trial was done to investigate the impact of vitamin A supplementation on diarrheal prevalence in children 1 to 5 years of age. Subjects given 200.000 IU of vitamin A at the first visited and 6 months afterward, were compared to subjects who did not receive vitamin A. Subjects were followed-up for 1 year. No significant difference in the prevalence of diarrhea in the two groups was observed.[8] In West Java, a trial on 1.407 preschool-age children (community-based) was done to measure the effects of vitamin A on incidence and duration of diarrhea. Subjects were children aged 6 to 47 months, who received either vitamin A (at WHO recommended doses) or placebo on their entry into the study and every 4 months thereafter until 24 months of observation. Serum retinol was measured before treatment and at the last follow-up visit. Serum retinol measurement at the time of enrollment revealed that 6% of subjects had very low levels, 52% had moderately low levels and the remainder of subjects had normal levels. In their last follow-up, the mean serum retinol of vitamin A group was 24% higher than that in the placebo group. However, vitamin A supplementation appeared to have no overall effect on the incidence or duration of diarrhea.[9]

Our study had several limitations. Outcomes assessment in our study were based on parents' or nanny's reports, not our own observations. However, since we applied a blinding intervention and assessment, we believe that even if misreporting did occur, it occured in random and thus very unlikely to cause a biased estimate other than the underestimation of effect size. Another limitation was that no stool examination were performed to establish the etiology of diarrhea. In addition, we did not assess the impact of other predisposing factors, such as mothers' educational level, water cleanliness, or environmental conditions that could influence the recovery processes.

In conclusion, vitamin A supplementation is effective in reducing the severity of acute diarrhea in children under five years of age.

References

1. Brown KH. Diarrhea and malnutrition. J Nutr. 2003; 133:328-32.
2. Mannick E, Zhang Z, Udall JN. Immunophysiology and nutrition of the gut. In: Walker WA, Watkins JB, Duggan C, editors. Nutrition in pediatrics. 3rd ed. Ontario: BC Decker Inc; 2003. p.341-57.
3. McCullough FS, Northrop-Clewes CA, Thurnham DI. The effect of vitamin A on epithelial integrity. Proc the Nutr Soc. 1999; 58:289-93.
4. Semba RD. Impact of vitamin A on immunity and infection in developing countries. In: Bendich A, Deckelbaum RJ, editors. Prevention nutrition: the comprehensive guide for health professionals. New Jersey: Humana Press; 1997. p.337-47.

5. Green HN, Mellanby E. Vitamin A as an anti-infective agent. BMJ. 1928; 3:691-6.

6. Scrimshaw NS, Taylor CE, Gordon JE. Effect of malnutrition on resistance to infection. In: Scrimshaw NS, Taylor CE, Gordon JE, editors. Interactions of nutrition and infection. Monograph series no 57:94. Geneva: WHO; 1968. p.60-140.

7. Grotto I, Mimouni M, Gdalevich M, Mimouni D. Vitamin A supplementation and childhood morbidity from diarrhea and respiratory infections: a meta-analysis. J Pediatr. 2003; 142:297-304.

8. Abdeljaber MH, Monto AS, Tilden RL, Schork A, Tarwotjo I. The impact of vitamin A supplementation on morbidity : a randomized community intervention trial. Am J Public Health. 1991; 81:1654-6.

9. Dibley MJ, Sadjimin T, Kjolhede CL, Moulton LH. Vitamin A supplementation fails to reduce incidence of acute respiratory illness and diarrhea in preschool-age indonesia children. J Nutr. 1996; 126:434-42.

10. Makmun D, Simadibrata KM, Abdullah M, Syam AF, Fauzi A, editors. Konsensus penatalaksanaan diare akut pada dewasa di Indonesia. Jakarta: Perkumpulan Gastroenterologi Indonesia; 2009. p.1-21.

11. Abba K, Sinfield R, Hart CA, Garner P. Antimicrobial drugs for persistent diarrhea of unknown or non-specific cause in children under six in low and middle income countries:systematic review of randomized controlled trials. BMC Infect Dis. 2009; 9:1-8.

12. Ashraf H, Rahman MM, Fuchs GJ, Mahalanabis D. Folic acid in the treatment of acute watery diarrhea in children:a double-blind, randomized, controlled trial. Acta Paediatr. 1998; 87:1113-5.

13. Fawzi WW, Chalmers TC, Herrera MG, Mosteller F. Vitamin A supplementation and child mortality: a meta-analysis. J Am Med Assoc. 1993; 269:898-903.

14. Fawzi WW, Herrera MG, Willett WC, Nestel P, Amin AE, Mohamed KA. Dietary vitamin A intake and the incidence of diarrhea and respiratory infection among Sudanese children. J Nutr. 1995; 125:1211-21.

15. Reddy V. History of the international vitamin A consultative group 1975-2000. J Nutr. 2002; 132:2852-6.

16. Salazar-Lindo E, Salazar M, Alvarez JO. Association of diarrhoea and low serum retinol in Peruvian children. Am J Clin Nutr. 1993; 58:110-3.

17. Kucukbay H, Yakinci C, Kucukbay FZ, Turgut M. Serum vitamin A and beta-carotene levels in children with recurrent acute respiratory infections and diarrhea in Malatya. J Trop Pediatr. 1997; 43:337-40.

18. Ahmed FU, Rahman ME, Mahmood CB. Vitamin A deficiency in children with acute diarrhoea:a community-based study in bangladesh. J Health Popul Nutr. 2000; 18:119-22

19. Stoll BJ, Banu H, Kabir I, Molla A. Nightblindness and vitamin A deficiency in children attending a diarrhoea disease hospital in Bangladesh. J Trop Pediatr. 1985;31:36-9.

20. Stanton BF, Clemens JD, Wojtyniak B, Khair T. Risk factors for developing mild nutritional blindness in urban Bangladesh. Am J Dis Child. 1986;140:584-8.

21. Thurnham DI, Northrop-Clewes CA, McCullough FS, Das BS, Lunn PG. Innate immunity, gut integrity, and vitamin A in Gambian and Indian infants. Infect Dis. 2000;182 Suppl 1:23-8.

22. Paracha PI, Jamil A, Northrop-Clewes CA, Thurnham DI. Interpretation of vitamin A status in apparently healthy Pakistani children by using markers of subclinical infection. Am J Clin Nutr. 2000; 72:1164-9.

23. Benn CS, Martins C, Rodrigues A, Jensen H, Lisse IM, Aaby P. Randomised study of effect of different doses of vitamin A on childhood morbidity and mortality. BMJ. 2005; 10:1-5.

24. Allen LH, Haskell M. Estimating the potential for vitamin A toxicity in women and young children. J Nutr. 2002; 132:2907-19.

25. Semba RD. Vitamin A and immunity to viral, bacterial and protozoan infections. Proc Nutr Soc. 1999; 58:719-27.

26. Biswas R, Biswas AB, Manna B, Bhattacharya SK, Dey R, Sarkar S. Effect of vitamin A supplementation on diarrhoea and acute respiratory tract infection in children. A double blind placebo controlled trial in a Calcutta slum community. Eur J of Epidemiol. 1994; 10:57-61.

27. Dewan V, Patwari AK, Jain M, Dewan N. A randomized controlled trial of vitamin A supplementation in acute diarrhea. Indian Pediatr. 1995; 32:21-5.

28. Bhandari N, Bhan MK, Sazawal S. Impact of massive dose of vitamin A given to preschool children with acute diarrhoea on subsequent respiratory and diarrhoeal morbidity. BMJ. 1994; 309:1404-7.