REPORT ON

VITAMIN A SYMPOSIUM

CENTRE
FOR HEALTH AND POPULATION RESEARCH

International Centre for Diarrhoeal Disease Research, Bangladesh
Mohakhali, Dhaka 1212, Bangladesh

REPORT ON
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TABLE OF CONTENTS

Introduction

The purpose of this one-day symposium was to disseminate the results of extensive research dealing with vitamin A. In recent years, these studies were undertaken by ICDDR,B and its collaborating national and international institutions and encompassed a wide spectrum including laboratory, clinical and community-based studies. The contents of this report include brief abstracts of each presentation, a brief summary of each of the three sessions, and recommendations on the programmatic and policy implications of the findings. Seventeen papers were presented, and one hundred and thirteen experts engaged in vitamin A research participated in the symposium.

Symposium Organizing Committee

Dr. AN Alam: Convener
Dr. KMA Aziz
Dr. AH Baqui
Mr. MSI Khan
Dr. SK Roy
Mr. MA Wahed
Dr. MA Khaled: Advisor

An inside view of the Sasakawa Auditorium during the symposium

PANEL RECOMMENDATIONS

A. Assessment of Vitamin A Status

1. Assessment of vitamin A status in an individual requires the employment of a combination of appropriate methods (more than one). No single method is found satisfactory for all instances.

2. More information is required on the magnitude of vitamin A deficiency in infants under 6 months of age.

B. Dietary Intake

1. Infants under 6 months of age can receive adequate amount of vitamin A from breast milk (if the content of vitamin A in the breast milk is adequate).

2. Improvement in intake of dietary sources of vitamin A is feasible in older infants and children, and should complement any programmes to control vitamin A deficiency.

3. Mothers should encourage adequate intake of carotene-rich foods by their children. Green leafy vegetables, rich in carotenoid, should be made available through home gardening. In high-risk areas, this programme should be supported by adequate and proper nutrition education.

C. Vitamin A Supplementation

1. Adequate levels of vitamin A can be ensured in breast milk by supplementation of a large dose (200,000 IU) of vitamin A to lactating mothers within six weeks (but not later) after delivery. Supplementation can be offered to mothers at the time of the first EPI visit of the infant.

2. In communities where vitamin A deficiency is known to occur in infancy, vitamin A should be provided at the 1st and 3rd EPI visit. Infants should be supplemented with 25,000 IU vitamin A at 6 weeks and repeated at 14 weeks.

   Supplementation for infants older than 6 months should follow existing recommendation.

3. Other modes of vitamin A delivery, such as micro-encapsulation, fortification of wheat, sugar and oil should be investigated keeping in mind the cost involved, adequacy of absorption and the wider coverage of the population. One of the cheapest techniques may prove to be fortification of salt.

Introductory Remarks by Mr. Richard Brown, Mission Director, USAID Dhaka

Mr. Brown observed that vitamin A deficiency, the principal cause of blindness in the developing world, is recognized as an important nutritional problem of public health significance. Considerable evidence has accumulated in recent years on the effect of vitamin A on child survival. Early studies showed that the mortality rate among children with mild vitamin A deficiency was several fold higher than among children without vitamin A deficiency. Subsequent studies have shown that supplementation of vitamin A to vitamin A-deficient young children reduces mortality by 20%-50%. Based on these findings, a WHO/UNICEF/IVACG Task Force has recommended vitamin A supplementation for improving child survival. The recommendations for countries where vitamin A deficiency is a public health problem (which include Bangladesh), require that each child between the age of 6 months and 6 years be supplemented with vitamin A every 6 months.

He said that the Government of Bangladesh has been implementing the national vitamin A programme, but so far, the coverage of vitamin A distribution has been modest. In contrast, another vertical programme (EPI) has achieved much better coverage, reaching almost every child in the country at least once. Thus, the time of immunization might be a good opportunity to supplement vitamin A and could be an effective short-term measure for achieving adequate vitamin A status in the first year of life. However, he said the safety and efficacy of vitamin A supplementation during early infancy have not been clearly documented. Supplementation with synthetic vitamin A is only a short- term measure.

He further said that long-term options, such as food fortification and promotion of vitamin A-rich foods need to be given adequate attention at the same time as we explore more effective ways of supplementing children with doses of vitamin A.

Chairpersons' Remarks

SESSION I

About 230 million children worldwide are estimated to have vitamin A deficiency, but the methods available to assess vitamin A status in man have significant limitations. Different techniques used for the purpose do not always correlate with each other on a one-to-one basis in an individual as they rely on very different parameters. For example, conjunctival impression cytology examines defects in the epithelial cells of the eye, isotope dilution methods examine total body stores, and hepatic retinol concentration rely on vitamin A content of a single organ when there may be no homogeneity of tissues. The modified relative dose response (MRDR) test as presently administered detects retinol-binding protein saturation at only levels lower than 50%, and serum level of vitamin A is altered by coexisting infection. Consequently, there is no single "gold standard" for the clinical assay of vitamin A status; ideally, at least two different assays should indicate the problem in the same direction if conclusions are to be drawn. Even with these limitations, if they are used together and appropriately, the magnitude of the vitamin A deficiency problem in the high-risk areas can be detected and intervention programmes can be evaluated by using a combined strategy of using at least two techniques.

SESSION II

In the past, programmes to improve dietary vitamin A status have not been very aggressive. Proper assessment of dietary intervention demands prior evaluation of dietary deficiency, validation of the role of foods rich in carotenoids and documentation of their impact considering the bioavailability and

the factors influencing it. Experience at ICDDR,B shows that green leafy vegetables alone can provide adequate dietary sources of vitamin A.

SESSION III

Under-nourished, deprived young infants have been shown to be deficient in vitamin A with few, if any, hepatic reserve but vitamin A supplementation has not improved the survival of these infants. Studies have failed to demonstrate significant effect of a single large dose (200,00 IU vitamin A) on the course and outcome of acute infections like pneumonia and shigellosis; the benefit of such a supplement in modifying the next episode of illness cannot be ruled out. Side-effects like bulging fontanelle, were observed in young infants under six months of age with repeated small doses (2500 IU vitamin A); however, most such episodes were transient lasting under 72 hours.

Mothers who accompany their sick children in the hospital receive practical training on dietary sources of vitamin A

APPENDIX
Abstracts

Assessment of Vitamin A Status

COMPARISON OF BIOCHEMICAL ASSESSMENT TECHNIQUES FOR VITAMIN A STATUS IN MALNOURISHED CHILDREN IN BANGLADESH

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Biochemical methods, such as serum retinol, the modified relative dose response (MRDR), and the relative dose response (RDR) were carried out on 50 Bangladeshi children, 5-36 months of age. Most of the children were mild to moderately malnourished but free of any apparent infections. Children were supplemented orally with either 100,000 (under 1 year) or 200,000 (over 1 year) IU of vitamin A after performing both MRDR and RDR tests. Of them, 40 children were followed up for biochemical measure of vitamin A status. Thirty-three children (67%) had low vitamin A stores according to the RDR, while only 9 (18%) were positive according to MRDR. Among 25 children with serum retinol levels lower than 20 μg/dl (0.7 μM), 92% was RDR positive, while only 40% was MRDR positive. When plotted against the anthropometric parameters, e.g. weight-age, weight-for-height and height-for-age, neither MRDR nor RDR showed any significant dependency on nutritional status.

Six weeks after supplementation, only 3 of 7 children (who were MRDR positive before supplementation) were found to have normal values (i.e. adequate vitamin A stores). Moreover, serum retinol (pre: 23.0 μg/dl; post: 22.6 μg/dl), serum RBP (pre: 2.0 mg/dl; post: 2.0 mg/dl) and serum transthyretin (pre: 12.5 mg/dl; post: 13.0 mg/dl) did not increase significantly 6 weeks after supplementation.

These data suggest that the sensitivity of the MRDR test to detect low vitamin A stores among malnourished children is significantly lower than that of RDR test. Thus, the MRDR test may be inadequate for use in populations where mild to moderate malnutrition is prevalent. Results also show that in malnourished children large oral supplements of vitamin A are either poorly absorbed and retained or are depleted in a relatively short period.

USE OF CONJUNCTIVAL IMPRESSION CYTOLOGY AS AN INDICATOR OF VITAMIN A DEFICIENCY IN YOUNG CHILDREN

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A comparative study was conducted on conjunctival impression cytology (CIC) with serum retinol, relative dose response (RDR) and modified relative dose response (MRDR) methods to detect subclinical vitamin A deficiency in 56 children under 3 years of age. The CIC, RDR, and MRDR were done on the same child. After obtaining parental consent, CIC samples from both eyes of the child were collected. Then MRDR test was performed and 3 days after the MRDR test, RDR test was done. Of the 56

children, 47 (84%) were normal, 7 (12.5%) were marginally normal, 2 (3.5%) were marginally abnormal, and none was deficient by CIC. The mean (SD) serum retinol (μg/dl) in the children with normal and abnormal CIC were 21.5 (± 8.8) and 22.2 (± 12.2) respectively. Using the criteria of serum retinol (cut off: 20 μg/dl), RDR (20% cut off) and MRDR (0.06 cut off) the number of vitamin A-deficient children were: 27 (5 of them had abnormal CIC), 23 (2 of them had abnormal CIC) and 10 (2 of them had abnormal CIC) respectively. The specificity (%) of CIC were 19 and 86 compared to serum retinol, 9 and 91 compared to RDR and 20 and 83 compared to MRDR. The results suggest that CIC does not have the ability to detect the subclinical vitamin A deficiency in children who had been diagnosed as vitamin A-deficient by serum retinol, RDR and MRDR.

COMPARISON OF INDIRECT METHODS OF ASSESSING VITAMIN A STATUS WITH HEPATIC VITAMIN A CONCENTRATION IN BANGLADESHI SURGICAL PATIENTS

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Indirect methods of assessing vitamin A status, including fasting plasma retinol concentration, the relative dose response (RDR) test, conjunctival impression cytology (CIC), and frequency of consumption of vitamin A-rich foods, were compared with the hepatic vitamin A concentration in 31 adult surgical patients (m=15, f=16) in Bangladesh. The patients were of low socioeconomic status, ranged in age from 21 to 65 years, and had

an average BMI of 17.7 ± 3.4 kg/m^2 (range: 14-27 kg/m^2). They were scheduled for elective abdominal surgery for peptic ulcer or gall bladder disease, but were otherwise not acutely ill. At the time of surgery a liver biopsy was obtained for measurement of the hepatic retinol concentration. The mean hepatic retinol concentration was 94 ± 59 nmol/g (25-245 nmol/g), and 14 subjects (45%) had hepatic concentrations of <70 nmol/g. The mean fasting plasma retinol concentration was 1.33 ± 0.42 µmol/l (0.59-2.34 µmol/l); 7 of the patients had concentrations of <1.05 µmol/l, and 1 had a concentration of <0.70 µmol/l. The concentration of C-reactive protein in serum was elevated (>12 mg/l) in 2 of the patients with low plasma retinol concentration (both <0.73 µmol/l). None of the patients had an RDR of >14%, and only 1 patient had abnormal conjunctival cytology in both eyes. Analysis of the dietary data has not yet been completed. A positive but non-significant relationship was observed between plasma and hepatic retinol concentrations among patients with plasma levels of <1.05 µmol/l (r^2=0.48, p=0.13, n=6); and a significant correlation between plasma and hepatic retinol concentrations was observed among subjects with hepatic concentrations of <70 nmol/g (r^2=0.34, p=0.04, n=14). The fasting plasma retinol concentration was the most useful indicator for identifying subjects with low liver stores of vitamin A. However, it did not consistently identify subjects with liver concentrations of <70 nmol/g.

MODIFIED RELATIVE DOSE RESPONSE (MRDR) IS HIGHLY DEPENDENT ON PERCENT SATURATION OF RBP

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The modified relative dose response (MRDR) is a test that uses didehydroretinol or vitamin A_2 (a naturally occurring analog of retinol) to measure liver stores of vitamin A indirectly. The use of this analog confers the MRDR an apparent advantage over the relative dose response (RDR) in that only one blood sample is required. A comparison of the MRDR and RDR tests among malnourished children in Bangladesh has demonstrated that the MRDR is significantly less sensitive than the RDR in detecting children with low vitamin A stores. In addition, we have detected a strong dependency of the MRDR test on the percent saturation of RBP (i.e. the percent of RBP bound to retinol). A plot of MRDR versus percent saturation of RBP showed a negative exponential (i.e. decay) curve where all positive MRDR values were basically restricted to an RBP saturation level lower than 50%. In fact, when RBP saturation was higher than 50%, didehydroretinol cannot effectively compete with retinol for RBP binding. Thus, under these circumstances the MRDR test is rendered ineffective.

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CAROTENE-RICH FOODS: PROMOTION OF SOME COMMON AND LESS FAMILIAR VEGETABLES AND MODIFICATION OF COOKING PROCEDURES IN RURAL BANGLADESH

KMA Aziz, M Yunus, RB Sack, and AI Chowdhury

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Intake of vitamin A in diets by young children in Bangladesh remains inadequate, and carotene loss is reported to be occurring in varying degrees during preparation and cooking process. These are the major causes of blindness among the young children. Vitamin A capsule distribution programme, currently being implemented in Bangladesh, is a short-term measure to prevent nutritional blindness among young children. The real solution to the problem of vitamin A deficiency in Bangladesh lies in increasing the consumption and improving the preparation process of vegetables rich in beta-carotene. This study developed a nutrition education strategy that is designed to lead to improved preparation and cooking methods of these vegetables and their increase in consumption. It was conducted in some rural communities of Matlab, Bangladesh, during July-December 1992.

The evaluation of compliance to the recommended preparation and cooking methods of these vegetables and their intake was done by Knowledge, Attitude and Practice surveys, 24-hour dietary recall and 8-hour on-site observation during food preparation and eating. One hundred and sixty children aged from 6 to 59 months drawn from 160 households of very poor socioeconomic status were studied. All the care-givers of target children received an educational intervention on vitamin A

containing vegetables and their preparation process at a monthly interval during the intervention period. The findings showed that the preparation and consumption of vegetables rich in beta-carotene were substantially improved in the post-intervention period compared to baseline data. Following the intervention, commonly available green leafy vegetable and the naturally grown, less familiar ones were consumed frequently and adequately by the young children in the target households.

Early adequate feeding of green leafy vegetables and advising care-givers on ways of serving should have a significant impact on the problem, especially during the first two years of life. The reluctance in feeding vegetables in early phase of life was overcome through an educational intervention in the study area.

ADEQUACY OF VITAMIN A INTAKE FROM SINGLE MEAL OF GREEN LEAFY VEGETABLES IN INFANCY AND CHILDHOOD

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The study was conducted to evaluate the feasibility of providing adequate vitamin A precursors to the infants and young children to meet their recommended daily allowance from a meal of traditionally cooked green leafy vegetables (GLV) and boiled rice. Mothers' perceptions and acceptance of the GLV were also evaluated. Mothers of 118 children, reporting to the nutritional follow-up unit of the International Centre for Diarrhoeal Disease Research, Bangladesh, were interviewed

regarding their acceptance and perceptions about giving GLV to their young children. Children were served a measured amount of rice and cooked GLV, and each mother was asked to feed her child as much as she could. Median intakes of GLV in children aged 6-11 months, 12-17 months and 18-35 months were respectively 41 g, 71 g and 129 g in terms of raw green leaf. Most intakes were more than 75% of the recommended daily allowance for the vitamin A precursors. Among the infants, 77% was breastfed and they had a lower intake compared to those completely weaned. Eighty-nine percent of the mothers liked to give vegetables to their children and 74% of them believed that vegetables were beneficial for health of their children. Eighty-seven percent of the children liked the meal and only 2 (1.5%) mothers refused to feed their children leafy vegetables. The results indicate that young children can eat enough leafy vegetables to meet their daily requirement of vitamin A. Considering the limitation that the study was conducted at hospital setting, we followed a subsample (n=44) of children who received demonstration on feeding, with hospital control (n=36) who received only health education and neighbourhood control (n=80) who did not receive any health education. Spot-checking of whether GLV was cooked and fed were made after 8 weeks at their homes without prior notice. The percentages of mothers who thought that GLV were good for health were: 89%, 86% and 76% in the three groups. However, the percentages of mothers who fed their children GLV on that day were: 57%, 64% and 26% in the three respective groups implying the positive impact of health education in promoting GLV feeding to young children.

OXIDATIVE STRESS AND ANTIOXIDANTS: IMPLICATIONS ON VITAMIN A STATUS IN MALNOURISHED CHILDREN

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Reactive oxygen species (ROS)-induced oxidative stress can be relieved by some essential exogenous antioxidants, namely beta-carotene, vitamin A, C and E. Vitamin A that maintains the structural integrity of various tissues and cells is usually depleted in malnutrition by the progression of ROS. Megadose vitamin A supplementation to malnourished children could therefore be ineffective unless the ROS production is inhibited. This contention has been supported by the results of a preliminary study that included 16 children recovering from diarrhoeal diseases divided into two groups: 8 of them received a high-protein diet for three weeks with no vitamin A supplementation (group A), while the other 8 children remained on the usual home-based diet and were given 200,000 IU vitamin A supplementation (group B). After about 3 weeks, the serum vitamin A, RBP, prealbumin and TBARS (Thiobarbituric Acid Reacting Substances as marker for oxidative stress) were measured and compared with their pre-supplemented values. The children in group A showed highly significant increases of RBP, prealbumin and vitamin A with concomitant reduction in the oxidative stress, i.e. lower TBARS values, while group B with insufficient protein intake did not show any appreciable change in these parameters. This significant increase in serum vitamin A of children in group A may be attributed to the antioxidative properties of the high-protein diet. Further studies are now necessary to investigate the mechanisms of antioxidant activity in malnutrition and infections.

BULGING FONTANELLE AFTER SUPPLEMENTATION WITH 25,000 IU VITAMIN A IN INFANCY USING EPI CONTACTS

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To evaluate the safety and toxicity of vitamin A supplementation in infancy using EPI contacts, a double-blind-randomized, placebo-controlled trial was conducted in urban Bangladesh. One hundred and sixty-seven infants received three doses of either 25,000 IU vitamin A or placebo at 6.5 ± 0.9, 11.8 ± 1.2, and 17.0 ± 1.3 weeks of age. Trained physicians examined each of the infants on days 1, 2, 3, and 8 after supplementation. Nine infants (10.5%) supplemented with vitamin A had episodes of bulging of the fontanelle as opposed to two infants (2.5%) in the placebo group ($p<0.05$). Twelve of the 14 episodes occurred in infants supplemented with vitamin A. Of the 12 episodes, none occurred with the first dose, three occurred with the second dose, and nine with the third dose, suggesting a cumulative effect of vitamin A toxicity. The incidence of bulging of the fontanelle with this lower dose of vitamin A was similar to that observed earlier with 50,000 IU. No other serious side-effects were observed.

VITAMIN A SUPPLEMENTATION GIVEN TO THE MOTHERS AFTER DELIVERY REDUCES INFANT MORTALITY AND INCREASES SYMPTOMS OF MORBIDITY

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Vitamin A supplementation of infants under 6 months of age has not been shown to influence mortality. Nevertheless, maternal vitamin A supplementation soon after birth is currently recommended as a potentially beneficial intervention. Morbidity and mortality of infants born to 3,790 mothers who were supplemented with 300,000 IU of vitamin A each shortly after delivery were compared with those of 4,945 infants who were born to mothers not supplemented. Apart from vitamin A supplementation, curative and preventive health services remained unchanged for the population. Infants were followed till 180 days after birth.

Non-breastfed infants experienced a high mortality rate and were excluded from the main analysis. Infants nursed by mothers supplemented around 60 days after delivery experienced a significantly lower mortality than their non-supplemented counterparts. Infants nursed by supplemented mothers presented a higher point prevalence of symptoms compatible with diarrhoea and acute lower respiratory infections (ALRI). No significant differences were detected on severity of ALRI episodes between supplementation groups. The mortality reduction reported here may be explained by improved vitamin A content of breastmilk. The results indicate that maternal vitamin A supplementation after delivery alongside promotion of breast feeding may be an effective strategy to lower mortality in communities with poor vitamin A status.

IMPACT OF LARGE DOSES OF VITAMIN A ON VITAMIN A STATUS OF YOUNG INFANTS

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We evaluated the safety and efficacy of 3 oral doses of 50,000 IU vitamin A at monthly intervals in predominantly breastfed infants from poor urban Bangladesh aged 6-17 weeks having DPT and oral polio vaccines in a randomized, double-masked controlled trial. Ninety-seven infants received vitamin A and 103 received placebo. Initial serum retinol levels (fasting) were very low in most infants (52% <10 μg/dl and 74% <15 μg/dl) which improved in both groups but was still less than 15 μg/dl in 30% of those who received vitamin A. Nine infants in the vitamin A group and 2 in the placebo group had bulging fontanelle after the second and/or third dose (RR=4.78, 95% CI 1.06-21.54, $p<0.025$) which resolved in 48 hours. It is concluded that young infants from a deprived urban community in Bangladesh were deficient in vitamin A; a large proportion remained deficient even after three large doses of vitamin A. In spite of deficiency, bulging fontanelle, an apparent toxic manifestation, occurred in 9% with this dosage schedule of vitamin A. Alternative and/or complimentary approaches, e.g. maternal supplementation, should be explored to prevent vitamin A deficiency among infants aged under 6 months in developing countries.

SINGLE MEGADOSE OF VITAMIN A DOES NOT ALTER THE CLINICAL COURSE OF ACUTE SHIGELLOSIS IN CHILDREN

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Vitamin A deficiency increases childhood mortality and morbidity possibly through increasing the severity of infectious diseases like dysentery. The objective of this study was to investigate whether a large dose of vitamin A can reduce the disease severity in patients suffering from acute shigellosis, from a population with a high rate of marginal vitamin A deficiency. A randomized, double-blind, placebo-controlled clinical trial was conducted on 62 children (aged 1-3 years) infected with bacteriologically proven shigellosis (vitamin A supplemented group: *S. dysenteriae* type 1 21, *S. flexneri* 11, control group: *S. dysenteriae* type 1 20, *S. flexneri* 19, *S. dysenteriae* type 2 one and *S. sonnei* one). The study started within 72 hours of illness and was carried out at the International Centre for Diarrhoeal Disease Research, Bangladesh, during July 1992-September 1993. The patients received a dose of vitamin A (200,000 IU) each either at entry or on exit in the study or control group respectively along with appropriate antimicrobial drugs. The patients were similar with regard to age, nutritional status, and severity of illness at admission. At the end of five days, outcome variables, such as absence of blood in the stool (46% vs 44%)), mean stool frequency (64 ± 45 vs 75 ± 50), absence of fever (86% vs 85%), absence of abdominal tenderness (83% vs 82%), improvement in appetite (56% vs 44%), physicians' impression as marked clinical improvement (72% vs 85%), bacteriological cure (67% vs 69%), were comparable between the two groups. These results show no differences in the clinical course of illness between vitamin A-supplemented and the control groups.

VITAMIN A SUPPLEMENTATION IN PNEUMONIA

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In a double-blind, randomized study, the effect of 200,000 IU vitamin A supplementation with standard case management was evaluated in hospitalized children with pneumonia. One hundred thirty children of both sexes, aged 7-60 months, admitted to Dhaka Shishu Hospital with fast breathing and/or chest indrawing with proven radiological evidence of pneumonia were enrolled. Admission characteristics of both groups of patients were comparable. Of the 130 patients, 108 cases were treated in hospital and were followed up fortnightly after discharge for a period of 3 months. Sixteen patients on completion of therapy in the hospital could not be followed up due to change in their residential address. Six cases developed complications, such as tuberculosis, pyopneumothorax and heart failure, and they were excluded from the study.

Patients were monitored closely for cough, respiration rate, body temperature, chest indrawing and presence of added sounds in the lung every 4 hours while in hospital, and then at each follow up after discharge. The result of preliminary analysis showed no significant effects of vitamin A supplementation on the course and outcome of pneumonia in children.

VITAMIN A SUPPLEMENTATION IN THE FIRST 6 MONTHS OF LIFE: DOES IT REDUCE DIARRHOEA AND ARI MORBIDITY?

SE Arifeen and AH Baqui

International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka, Bangladesh

The study presents the results of a double-blind, randomized, placebo-controlled trial evaluating the efficacy of vitamin A supplementation in early infancy using EPI contacts. The study was conducted in an urban poor population in Bangladesh. One hundred and twenty-one infants received 3 doses of vitamin A and another 125 children were given a placebo at the three recommended EPI contacts. Since the dose of vitamin A was reduced during the study, about 7% received 3 doses of 50,000 IU each and the remaining received at least one dose of 50,000 and 25,000 IU. The infants were visited every fortnight to collect information on the occurrence of diarrhoea and respiratory infections. Univariate and standard multivariate analyses revealed no significant morbidity differences between the supplemented and placebo groups. However, there was a consistent pattern of slightly higher, but nonsignificant, risk of diarrhoea and respiratory infections among the supplemented infants. The possibility of increased risk of morbidity is consistent with the recently published reports which may have significant policy implications.

Poster Presentation

VITAMIN A LEVELS IN BREASTMILK AFTER SUPPLEMENTATION TO MOTHERS AFFECTING MORBIDITY OF THE BREASTFED INFANTS

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Vitamin A is essential for normal vision, growth, reproduction, immune response and the maintenance of integrity of epithelial structures. A close relationship between mild vitamin A deficiency and diarrhoeal morbidity and mortality has also been reported from Indonesia. The role of vitamin A deficiency in causing morbidity in vitamin A-deficient breastfed infants is unknown. To examine the possible impact on growth, we studied a group of mothers and children from the very low-income groups living in periurban villages, Nandipara, Dhaka. Mothers were given a 200,000 IU vitamin A each or placebo at delivery, and weekly morbidity and monthly anthropometric measurements were recorded for a year. Vitamin A concentration in the breastmilk remained significantly higher for 6 months in the supplemented mothers. The growth rates of the infants were not different between the groups. Infants of the supplemented mothers had significantly fewer episodes of respiratory tract infections and febrile days but diarrhoeal episodes were equal. The study suggests limited benefits of vitamin A supplementation in malnourished mothers for growth of their breastfed infants.

VITAMIN A SUPPLEMENTATION (50,000 IU) IS ASSOCIATED WITH BULGING OF THE FONTANELLE WHEN GIVEN WITH VACCINES IN INFANCY

A de Francisco, J Chakraborty, HR Chowdhury, Md Yunus, AH Baqui, AK Siddique, and RB Sack

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Vitamin A supplementation is being considered for delivery through the Expanded Programme on Immunization (EPI) to improve both vitamin A stores in liver, and increase its coverage in infants. To date, however, the effects of such supplementation have not been described. A double-blind, randomized, placebo-controlled trial was conducted in rural Bangladesh to evaluate the safety and toxicity of vitamin A supplementation in young infants through EPI. One hundred and ninety one infants were supplemented with either 50,000 IU vitamin A or a placebo at a mean age of 6.5, 11.1 and 15.8 weeks. Infants were examined on days 1, 2, 3 and 8 after supplementation.

A total of 11 infants (11.5%) supplemented with vitamin A had bulging of the fontanelle as opposed to 1 (1%) in the placebo group ($p<0.001$). There was a tendency toward a cumulative effect of toxicity with increasing doses. Although most such episodes were transient, bulging of the fontanelle lasted up to 72 hours in two infants. No other side-effects were noted during the period of observation. The results of this study indicate that repeated vitamin A supplementation to infants under six months of age at the dose used, together with EPI, increases the likelihood of toxicity and should therefore be avoided.

SUN-DRIED GREEN LEAFY VEGETABLES CAN PROVIDE ADEQUATE VITAMIN A FOR POOR COMMUNITIES

MM Rahman, **MA Wahed**, D Mahalanabis, and RB Sack

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Green leafy vegetables (GLV) contain high concentration of beta-carotene or provitamin A. In Bangladesh GLVs are abundant, yet vitamin A deficiency is a major health problem. There are a number of reasons for this. The way GLVs are cooked may be one of such factors, since sufficient amount of beta-carotene may be lost in the cooking process. To avoid a high loss of beta-carotene during conventional cooking, GLVs were dried and after grinding, the powder was preserved in amber glass containers. A study was conducted to determine the loss of beta-carotene from GLVs after different methods of drying. Two varieties of GLVs containing high amounts of beta-carotene were purchased from a local market from January to September 1992; these were dried under different conditions and the beta-carotene content was estimated. The methods of drying were: oven drying at 60°C for 82 hours (Method I); sun-drying with a fine cloth as a cover to protect from direct sun light (Method II); sun-drying without a cover (Method III). After drying, the GLVs were ground, sieved and stored. Estimates of beta-carotene from fresh and dried vegetables were done monthly over a period of three months. The beta-carotene content of 100 g dried *Pat Sak* (*Chorchorus capsularis*) and *Lal Sak* (*Amaranthus gangeticus*) by Methods I, II and III were 60.40 and 58.70 mg, 51.45 and 49.65 mg, 40.4 and 39.0 mg, respectively. The beta-carotene contents of equivalent amounts of fresh *Pat Sak* and *Lal Sak* were 62.8 and 59.3 mg, respectively. It is calculated that only 5 g of dried *Lal* or *Pat Sak* (Method II) which contains 0.418-0.492 mg retinol equivalent, is adequate to meet the daily recommended vitamin A intake (0.4 mg/d) for a preschool child.

THE EFFECT OF RETINOL AND BETA-CAROTENE SUPPLEMENTATION IN LACTATING WOMEN ON BREASTMILK QUALITY AND VITAMIN A STATUS OF INFANTS

Amy Rice[1], C Kjolhede[1], A de Francisco[2], J Chakraborty[2], MA Wahed[2], and R Stoltzfus[1]

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To investigate the efficacy of maternal vitamin A supplementation for improving the vitamin A status of lactating women and their breast feeding infants, an individually randomized, double-masked, placebo-controlled trial is currently underway in Matlab. Lactating women and their newborn infants (n=220 pairs) were enrolled at 2 weeks (1± week) postpartum during July-September 1994. Mothers were randomized to receive either a one-time dose of 200,000 IU retinol, daily doses of 7.8 μg beta-carotene or daily placebo capsules during the nine month follow-up period of the trial. To evaluate the effects on maternal and infant vitamin A status, serum retinol and beta-carotene levels will be measured and the MRDR test conducted on a random sample (n=110) of the women at each visit (0.5, 3, 6 and 9 months) and on all infants at six months of age. Breastmilk samples collected from all women during each visit will be analyzed for their retinol and beta-carotene content. We hypothesize that both maternal retinol and beta-carotene supplementation will increase the vitamin A content of breastmilk and improve vitamin A status in mothers and infants.

VITAMIN A SYMPOSIUM

31 October 1994

SASAKAWA INTERNATIONAL TRAINING CENTRE

International Centre for Diarrhoeal Disease Research, Bangladesh

Mohakhali, Dhaka 1212, Bangladesh

PROGRAMME SUMMARY

Time			Event
8:30 a.m.			Registration
9:00 a.m.			Opening Ceremony
9:45 a.m.			Tea/Coffee
10:15 a.m.	**Session I**	:	Assessment of Vitamin A Status: Methodological Issues
11:30 a.m.	**Session II**	:	Dietary Approaches to Improve Vitamin A Status
12:30-1.30 p.m.			Lunch

1:30 p.m.	**Session III**	:	Effect of Large Doses of Vitamin A on Health: Administration During Infancy and Childhood
3:30-3:45 p.m.			Tea/Coffee
3:45 p.m.	**Session IV**	:	Panel Discussion: Programmatic and Policy Implications

POSTER PRESENTATIONS

PROGRAMME DETAILS

10:15 a.m. SESSION I

ASSESSMENT OF VITAMIN A STATUS: METHODOLOGICAL ISSUES

Chairperson: Dr. Barbara A Underwood
Special Advisor
on Vitamin A Programme
Nutrition Unit, WHO, Geneva,
Switzerland

SCIENTIFIC PAPERS

Title	Authors	Time
1. Comparison of Biochemical Assessment Techniques for Vitamin A Status in Malnourished Children in Bangladesh	MA Wahed MM Rahman MA Khaled et al.	15 min
2. Use of Conjunctival Impression Cytology as an Indicator of Vitamin A Deficiency in Young Children	MM Rahman D Mahalanabis MA Wahed et al.	15 min

Session I continues.....

Title	Authors	Time
3. Comparison of Indirect Methods for Assessing Vitamin A Status with Hepatic Vitamin A Concentration in Bangladeshi Surgical Patients	MJ Haskell GJ Handelman JM Peerson et al.	15 min
4. Modified Relative Dose Response (MRDR) is Highly Dependent on Percent Saturation of RBP	JO Alvarez MA Wahed D Mahalanabis et al.	15 min
DISCUSSION		15 min

11:30 a.m. **SESSION II**

DIETARY APPROACHES TO IMPROVE VITAMIN A STATUS

Chairperson: Dr. Frances R Davidson
Office of Health and Nutrition, USAID
Washington, DC, USA

SCIENTIFIC PAPERS

Title	Authors	Time
5. Carotene-rich Foods: Promotion of Some Common and Less Familiar Vegetables and Modification of Cooking Procedures in Rural Bangladesh	KMA Aziz M Yunus RB Sack et al.	15 min
6. Adequacy of Vitamin A Intake from a Single Meal of Green Leafy Vegetables in Infancy and Childhood	MM Rahman D Mahalanabis MA Islam et al.	15 min
7. Oxidative Stress and Antioxidants: Implications on Vitamin A Status in Malnourished Children	MA Khaled I Kabir MA Wahed et al.	15 min
DISCUSSION		15 min
12:30-1:30 p.m.	Lunch	

1:30 p.m. **SESSION III**

EFFECT OF LARGE DOSES OF VITAMIN A ON HEALTH: ADMINISTRATION DURING INFANCY AND CHILDHOOD

Chairperson: Dr. Donald S McLaren
Professor of Preventive Ophthalmology
Institute of Ophthalmology
University of London
International Centre for Eye Health, UK

SCIENTIFIC PAPERS

Title	Authors	Time
8. Bulging Fontanelle After Supplementation With 25,000 IU Vitamin A in Infancy Using EPI Contacts	AH Baqui A de Francisco SE Arifeen et al.	15 min
9. Vitamin A Supplementation Given to Mothers After Delivery Reduces Infant Mortality and Increases Symptoms of Morbidity	A de Francisco Y Yasui J Chakraborty	15 min

Session III continues.....

Title	Authors	Time
10. Impact of Large Doses of Vitamin A on Vitamin A Status of Young Infants	D Mahalanabis MM Rahman MA Wahed	15 min
11. Single Megadose of Vitamin A does not Alter the Clinical Course of Acute Shigellosis in Children	S Hossain D Mahalanabis D Habte et al.	15 min
12. Vitamin A Supplementation in Pneumonia	ATM Azharul Huque AN Alam MS Akbar et al.	15 min
13. Vitamin A Supplementation in the First 6 Months of Life: Does It Reduce Diarrhoea and ARI Morbidity?	SE Arifeen AH Baqui	15 min
DISCUSSION		20 min
3:30-3:45 p.m.	Tea/Coffee	

3:45 p.m. **SESSION IV**

PANEL DISCUSSION: PROGRAMMATIC AND POLICY IMPLICATIONS

Chairperson: Prof. Demissie Habte
Director, ICDDR,B

Discussants:
1. Dr. Barbara A Underwood
2. Dr. Donald S McLaren
3. Dr. Frances R Davidson

POSTER PRESENTATIONS

Title	Authors
1. Vitamin A Levels in Breastmilk After Supplementation to Mothers Affecting Morbidity of the Breastfed Infants	SK Roy A Islam A Molla et al.
2. Vitamin A Supplementation (50,000 IU) is Associated With Bulging of the Fontanelle When Given With Vaccines in Infancy	A de Francisco J Chakraborty HR Chowdhury et al.
3. Sun-dried Green Leafy Vegetables Can Provide Adequate Vitamin A for Poor Communities	MM Rahman MA Wahed D Mahalanabis et al.
4. The Effect of Retinol and Beta-carotene Supplementation in Lactating Women on Breastmilk Quality and Vitamin A Status of Infants	Amy Rice C Kjolhede A de Francisco et al.