Vitamin A status, other risk factors and acute respiratory infection morbidity in children

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Objective. This study evaluated the association between vitamin A status and the severity of acute respiratory infections (ARIs) in children, controlling for the influence of other known ARI risk factors.

Design. Case control study.

Setting. Ambulatory and hospital-based study.

Patients. Severe cases ($N = 35$) were children with ARI who were admitted to hospital for inpatient treatment, while mild cases ($N = 32$) were children with ARI who were treated as outpatients. The control group ($N = 54$) was selected from children with non-infectious diseases attending the outpatient department. Cases and controls were matched for age and area of residence.

Main outcome measures. Serum vitamin A levels and analysis of ARI risk factors.

Results. The mean (SD) vitamin A levels were 22.09 (7.27) µg/dl for the controls, 20.27 (11.11) µg/dl for the mild cases and 13.79 (7.60) µg/dl for the severe cases. All pairwise comparisons of levels of the three patient groups achieved statistical significance — severe and mild ($P < 0.01$), severe and control ($P < 0.001$) and mild and control ($P = 0.03$). After vitamin A levels were dichotomised, the odds ratios (and 95% confidence intervals) for severe versus mild cases were 2.1 (0.8 - 5.6), for mild versus controls 2.9 (0.8 - 10.5) and for severe versus controls 6.0 (2.0 - 19.4). A χ^2 for trend across the three groups was 13.2 ($P = 0.001$). Risk factors significantly associated with disease status included a history of hospital admission in the preceding 6 months, absence of a clinic card, poor housing and lack of electricity for indoor fuel use. Factors associated with poor vitamin A status included low weight for age, previous diarrhoeal disease and poor housing. Vitamin A status was independently associated with disease status in logistic regression modelling.

Conclusion. Vitamin A status has a strong association with severity of infection. The gradient of that association suggests a dose-response effect. The multifactorial nature

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of ARI severity and vitamin A status highlights the need for a comprehensive approach to public health programmes to address ARI. The role of vitamin A supplementation for at-risk groups is supported by this study, but needs to be clearly defined within a broader approach to health.

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The last decade has seen an increasing awareness that acute respiratory infection (ARI) is a major problem in developing countries.[1-3] ARI, along with diarrhoeal disease, is the most important cause of preventable deaths in children.[4] It causes more than one-third of all deaths in children under 5 years of age in many countries, frequently surpassing diarrhoeal disease. Almost half of all deaths in children under 5 in Africa are caused by ARI.[5,6] Differences in ARI epidemiology between developed and developing countries appear to be related to the severity of ARIs rather than the incidence.[2,7]

ARI is a major health problem for South African children, in terms of morbidity and mortality.[8] ARI mortality rates are 7 - 270 times greater in South Africa than in Western Europe. In the Western Cape ARI mortality exceeds that from diarrhoea. It is also the commonest reason for health service utilisation.[9,10]

Risk factors associated with increased susceptibility to and increased mortality from ARI include younger age, male gender, poor nutritional status (in particular, poor vitamin A status), poverty, household crowding, indoor and outdoor air pollution, lack of refuse removal, maternal smoking and short duration of breast-feeding.[7,11] Many of these factors are interrelated and it is difficult to separate their effects.

Vitamin A status has long been known to be associated with infection.[12,13] Poor vitamin A status has been shown to increase ARI mortality and morbidity (defined as incidence).[14-16] Vitamin A supplementation in selected groups has been shown to decrease ARI incidence, duration and severity.[17-19] Poor vitamin A status has therefore been identified as an important risk factor amenable to intervention.

Current international research is focusing on the effects of vitamin A supplementation on mortality and occurrence of infectious diseases, in particular ARI and gastro-enteritis, in children. None has examined the relationship between vitamin A status and severity of illness. In South Africa, despite evidence of vitamin A deficiency in local children,[20] its relationship with ARI mortality and morbidity has not been investigated (with the notable exception of measles-related ARI[19]). This study was undertaken to assess the relationship between vitamin A status and ARI morbidity in children.

Method

This was a case control study. The study population consisted of children under 5 years of age attending Red Cross War Memorial Children's Hospital. ARI cases were defined as children presenting with symptoms of a cough and fever of less than 14 days' duration. Severe cases were children who fulfilled these criteria and were admitted to hospital for inpatient treatment. Mild cases were children fulfilling the criteria but treated as outpatients. The use of admission criteria to categorise patients according to severity was validated by the researchers doing a clinical examination of the child and compiling an independent assessment of severity.

The researchers selected all severe cases admitted to hospital via the acute admissions ward during the study period. They served as index cases to which the mild cases and controls were matched for age and area of residence. The control group was drawn from children with non-infectious diseases who attended the outpatient department.

Sample size was calculated using the two-sided test for comparing the means of normally distributed samples of equal size. Sample size calculations sought to detect a 6 µg/dl difference in vitamin A levels, using a significance level of 0.01 and power of 90%. A sample of 30 was needed. The severe cases were used as index cases, and group matching was used to obtain mild and control cases with a similar age range, sex ratio and area of residence. A clinical examination was done on all the children. A questionnaire was administered to the primary caretaker of the child to document demographic data and other possible ARI risk factors. The questionnaire was administered to caretakers of 97 of the children in the study. This group included all 67 cases and 32 controls. An additional 22 controls were recruited from a well-baby clinic where the full questionnaire was not administered, but from whom basic demographic details and serum samples were obtained.

A sample of blood was collected from each child for retinol estimation, which was determined by high-performance liquid chromatography. The field work (clinical examinations, questionnaire administration and taking of blood samples) was done by two of the researchers (LD, JH), and the processing of all the samples by a third researcher (GK) in the hospital research laboratory. Repeatability of the vitamin A measurements was checked by repetition of the analysis of 10% of the samples. The study was approved by the Ethics and Research Committee of the University of Cape Town. Informed consent was obtained for all subjects.

Data analysis

The three groups (severe, mild and controls) were compared to assess whether they differed in their demographic characteristics, anthropometric indicators, vitamin A status and other risk factors for ARI.

The distribution of continuous variables was examined, and the means were compared using the appropriate parametric and non-parametric tests. The frequencies of the categorical variables were assessed in the whole sample, and in each of the three disease categories (severe, mild and controls). Contingency tables were used to calculate χ^2 values and odds ratios to evaluate associations between the risk factors and the disease categories. The continuous variables were dichotomised as follows in order to calculate relative risks: (*i*) age < or ⩾ 12 months; (*ii*) weight for age, height for age, weight for height about the sample means for each of these variables; (*iii*) vitamin A levels, < or ⩾ 20 µg/dl (the cut-off point between normal and low serum vitamin A levels[21]), duration of illness < or ⩾ 7 days, and breastfeeding duration < or ⩾ 3 months.

The criteria for these categories were based on international standards for vitamin A,[21] but for the other variables convenient points of reference were used to allow for adequate numbers within the strata of 2 x 2 tables. The means of the anthropometric measurements were used to categorise them. Very few children fell below the 50th centile for weight for age and height for age, and when stratified into severe, mild and controls, some of the strata contained zeros. It was felt that using the means of each of these variables would be a suitable alternative.

For calculation of odds ratios, categorical variables that had more than two categories were also dichotomised. Such variables included the housing (shack and single-room dwelling as opposed to rented and owned houses), fuel (electricity versus gas, paraffin, coal and wood).

Analysis of the data was by means of the Epi-Info Version 5.00 and SAS programmes. The Kruskal-Wallis test was used to compare the means of the samples. Contingency tables (χ^2 and odds ratios) were used to assess associations between variables. Multiple and logistic regression analyses adjusted for confounders and effect modifiers were used to estimate the independent impact of vitamin A status on outcome.

Results

A total of 121 children were enlisted in the study — 35 with severe ARI, 32 with mild ARI and 54 controls. There were 76 boys (62.8%) and 45 girls (37.2%). Ages ranged from 2 to 60 months, with a median of 13 months.

Descriptive information on the three groups is shown in Tables I and II. Table I shows the means and standard deviations of the age and anthropometric measurements in the whole combined sample, and in the three subgroups. The comparison of the age and anthropometric indicators across the groups shows that there is statistically significant variation in the distribution of weights for age and height for age across the groups. Table II describes risk factors by disease categories.

The association between risk factors and severity of ARI was determined by calculating the odds ratios for all the factors in Tables I and II. Significant differences in risk were evident between the severe and mild cases in respect of possession of a clinic card (OR = 3.4; 1.0 - 11.5) and housing conditions (OR = 4.2; 1.3 - 14.5). Mild cases were more likely to have had a previous ARI than the controls (OR 3.2; 1.0 - 10.1). The mothers of severe cases were more likely to be under 20 years old (OR 9.9; 1.1 - 228), and the severe cases were more likely to have had a previous admission (OR = 5.5; 1.2 - 33.4), poorer housing conditions (OR = 7.9; 2.2 - 29.9) and not to have electricity (OR = 4.9; 1.6 - 16.2) than the controls. The lower limit of many of these odds ratios, however, is approximately 1, and caution is advised in interpreting the risk levels on this basis.

Fuel use was analysed further, given that 45% of severe cases were noted to use paraffin or wood compared with 28% of mild cases and 12% of controls. The relative risk comparing severe cases and the other two groups combined was 2.37 (1.4 - 4.0) ($P = 0.002$). The use of paraffin and wood was therefore associated with an increased risk of severe ARI in the study sample.

None of the children examined had ocular evidence of vitamin A deficiency. Details of the vitamin A levels in the three groups are summarised in Table III. The mean vitamin A levels of the severe cases (13.79 µg/dl) were in the low range, while the mild cases (20.27 µg/dl) and the controls (22.09 µg/dl) were within the normal range. Ten (28.6%) of the severe cases had levels < 10 µg/dl, whereas only 1 (2.0%) of the controls and 3 (9.0%) of the mild cases had similar levels.

Table I. Demographic and anthropometric profile

	Total	Severe	Mild	Control	P*
No.	121	35	32	54	
Sex ratio	1.7	2.2	1.5	1.6	
Age (months)†	19.5 (15.7)	16.4 (9.8)	21.1 (15.8)	20.5 (18.5)	0.67
Weight for age†	97.9 (14.6)	92.3 (15.2)	98.2 (12.0)	101.4 (14.7)	0.03
Height for age†	98.5 (5.7)	96.8 (5.6)	98.2 (3.5)	100.7 (7.1)	0.05
Weight for height†	101.9 (13.3)	100.4 (14.5)	104.1 (11.9)	101.3 (13.5)	0.42

* Kruskal-Wallis test.
† Figures represent mean (SD).
The 50th percentile was the standard used to calculate weight and height (new NCHS standard).

Table II. Risk factors by disease status

	Total	Severe	Mild	Control
No.	97	33	32	32
Mother as care-giver	84 (85%)	29 (88%)	29 (91%)	26 (81%)
Mother's age (yrs)*	27.6 (6.3)	27.3 (4.3)	27.1 (6.5)	28.5 (7.5)
Days ill*	4.8 (3.7)	4.2 (3.6)	5.3 (3.8)	
Previous ARI†	45 (46%)	14 (42%)	20 (62%)	11 (34%)
Previous diarrhoea†	20 (21%)	10 (30%)	7 (22%)	3 (9%)
Previous admission‡	22 (23%)	12 (36%)	7 (22%)	3 (9%)
Clinic card seen	58 (60%)	17 (52%)	25 (78%)	17 (53%)
Breast-fed (< 3 months)	50 (52%)	18 (55%)	14 (44%)	18 (56%)
Housing¶	35 (35%)	20 (60%)	9 (28%)	6 (19%)
Fuel§	68 (70%)	17 (52%)	23 (72%)	28 (87%)
Adults/household*	4.2 (2.6)	4.2 (2.9)	4.0 (2.2)	4.3 (2.6)
Children/household*	2.8 (1.5)	2.9 (1.7)	2.4 (1.2)	2.9 (1.6)
Persons per room*	2.2 (1.3)	2.2 (1.3)	2.4 (1.6)	1.8 (1.0)
Mothers who smoke	29 (30%)	8 (24%)	7 (22%)	14 (44%)

* Mean (SD).
† In preceding 3 months.
‡ In preceding 6 months.
¶ Shacks and single rooms v. house occupancy.
§ Homes using electricity as main fuel source v. homes using gas, paraffin, wood or coal as main fuel.

Table III. Vitamin A status

	Control	Mild	Severe	*P*-value*
No.	54	32	35	
Mean	22.09	20.37	13.79	0.000001
SD	7.27	11.11	7.60	
Median	20.95	17.90	12.40	
IQ range	8.4	8.65	8.0	
P-value	0.026	0.004	< 0.001	

* Kruskal-Wallis test for 2 groups.

The comparison of the means of the vitamin A levels between the three groups showed that they differed significantly in the distribution of the levels (Table III). The mean vitamin A levels of clinic controls (21.1 µg/dl) did not differ from that of the hospital controls (21.8 µg/dl).

The above analysis does not assess the risk of being deficient if one has mild or severe ARI. Vitamin A was stratified and odds ratios were calculated comparing those patients with low (< 20 µg/dl) vitamin A levels and those with normal (≥ 20 µg/dl) vitamin A levels. The odds ratios were all greater than 1. However, comparison of the severe and the mild cases (OR = 2.1; 0.8 - 5.6) and the mild cases and the controls (OR = 2.9; 0.8 - 10.5) did not show a significant difference in risk (range for confidence interval included one). The severe cases were, however, at greater risk of being deficient than the controls (OR = 6.0; 2.0 - 19.4).

A χ^2 test for trend was calculated across a 3 x 2 table of vitamin A status (< or ≥ 20 µg/dl) and disease status with a χ^2 of 13.2 and *P*-value of 0.001. This indicates that there is a dose-response relationship between vitamin A status and disease outcome.

Multiple logistic regression using stepwise and backwards selection models comparing cases (severe and mild) and controls in respect of 12 variables, and 5 interaction terms for vitamin A and age, gender and anthropometric indices was performed (choice based on association found between these variables and vitamin A status). The Akaike Information Criterion was used to identify the best fit model. The odds ratios for the best fit model show that vitamin A is independently associated with disease status (Table IV). Variables which were rejected by the model were gender, anthropometric indices, mother's age, possession of a clinic card, previous diarrhoea, previous admission, parental smoking, type of housing and the interaction terms for vitamin A. Vitamin A status, age, fuel use and previous ARI remained in the model.

Table IV. Multiple logistic regression

	Odds ratio	95% CI	*P*-value
Vitamin A	3.4	1.1 - 10.5	0.016
Age (< or ≥ 12 months)	5.0	1.4 - 18.1	0.027
Fuel (electricity v. other)	3.5	0.9 - 12.9	0.056
Previous ARI	0.2	0.1 - 0.8	0.022
Overall model			0.0016

* Best fit model = vitamin A status, age, fuel, previous ARI.
Continuous variables were dichotomised as detailed in the text.

Age acted as an effect modifier with older children having a higher OR (4.67) for vitamin A deficiency than children less than 12 months old (2.19).

The two interviewers made every attempt to reduce interviewer bias, and a comparison of the two groups interviewed showed no differences. A 10% sample of the sera was randomly selected for repeat vitamin A measurement in the same laboratory. The Wilcoxon signed rank test showed no difference between the initial and the repeat readings.

Discussion

The study aimed to determine whether a difference in vitamin A status existed between children with differing ARI severity. The results indicate that as a group, children with severe infections have lower serum vitamin A levels than children with mild ARI. In addition, both these groups have significantly lower levels than the control group. There was also evidence of a gradient in the relationship between vitamin A status and severity of the ARI.

The severe cases were at greater risk of being vitamin A deficient than controls. However, severe cases were not more likely to be deficient than mild cases; neither were mild cases more likely to be deficient than the controls. As the study sample was calculated to compare the distribution of vitamin A between the groups, it did not take into consideration numbers needed for proportional risk estimation. Small numbers probably influenced the results of these calculations, and differences may well have been found had a larger sample been used.

Whether vitamin A deficiency was causally related to severity of pneumonia or whether the low vitamin A levels were the result of the severity of infection is debatable. The study was not designed to answer this question. Nevertheless, given the available evidence, particularly the studies that have shown that vitamin A deficiency is associated with an increase in the incidence of pneumonia,[14-16] and that vitamin A therapy does impact positively on ARI morbidity,[18,19] the results of this study would support the use of vitamin A therapy in the treatment of pneumonia.

The results of the evaluation of other risk factors confirmed findings of previous studies for factors such as fuel use, housing and maternal age.[7,11] Known risk factors such as breast-feeding duration, crowding and maternal smoking were not found to be significantly associated with ARI in this study. Information bias could have resulted from recall or reporting bias on the part of mothers — the possibility exists that cigarette smoking was underreported because of previous warnings at health services of the association between their smoking habits and ARI in their children. Similarly, breast-feeding may have been overestimated. It was not possible, however, to re-interview the child-minders and their responses were therefore not validated. Other factors which may have influenced the levels of cigarette smoking reported by the mothers is the level of urbanisation, with the severe cases appearing (given type of housing and fuel use) to be less urbanised than the mild cases and controls. From previous South African studies it is known that cigarette smoking rates are low

among black women in particular and this may be reflected in the findings.

Other unexpected findings were that children with severe ARI reported shorter duration of illness whereas one would have expected a longer duration of illness. This finding could be biased by the differing perceptions of ill health, with these mothers allowing the illness to progress before recognising it as serious. They could also have underreported the duration of the illness to avoid blame for the delay in seeking care. Alternatively, because of predisposing factors, disease may in fact proceed more rapidly to cause severe illness in these children.

Factors not previously listed as risk factors in the literature, but which were significant in this study, were previous admissions, previous ARI and the lack of a clinic card. The lack of a clinic card probably indicates poor contact with health services. Conversely, previous admissions and previous ARI suggest that children with severe ARI have a history of recurrent illnesses.

Of interest is the relationship between vitamin A status and other ARI risk factors. The association with other nutritional indices, in particular weight for age, is to be expected. However, the association with previous diarrhoeal disease, in the absence of an association with previous ARI, is of interest. This implies that diarrhoeal disease causes greater depletion of vitamin A stores than ARI. Vitamin A supplementation programmes have shown that diarrhoeal disease has a greater impact on mortality than ARI.[17]

The association with housing is more complex. Type of housing may simply be a proxy for poverty, and in the absence of detailed information about other factors such as household income and food intake, it is difficult to postulate what the mechanisms for this association are.

The multiple logistic regression revealed that vitamin A was independently associated with disease status in the presence of other risk factors. The other factors that remained in the model (age, fuel use and previous ARI) are also important determinants of ARI. Of these, vitamin A status and fuel use are amenable to direct intervention. The role of paraffin as an indoor fuel is particularly emphasised, and the need for alternative fuel sources must be a priority. The added risks of paraffin ingestion support this. The age effect clearly indicates that if supplementation programmes are introduced the target groups should not be children under 1 year as proposed, but rather the slightly older age group.

Interventions for vitamin A deficiency may take the form of supplementation programmes or a broader nutritional and socio-economic approach. Debates in the literature revolve around the 'magic bullet' approach: vitamin A supplementation is seen as an effective intervention while the addressing of socio-economic and other factors is far more complex and long-term.[22] Others argue that a more comprehensive strategy of food fortification, better diet, health education and horticultural activities, as well as the addressing of the issues of poverty and the environment, are the approaches to be followed.[23,24] Support for the more selective approach comes from a number of community-based supplementation studies.[25-29]

A meta-analysis has shown that vitamin A supplementation in both hospital and community situations has a positive effect on overall mortality.[17] The effect of supplementation on pneumonia-specific mortality was significantly protective in the hospital-based studies (OR 0.37; 0.20 - 0.69). The community-based studies, however, showed no effect of supplementation on pneumonia-specific mortality (OR 0.96; 0.65 - 1.42). Morbidity studies have also had conflicting results. Supplementation studies of selected high-risk groups have shown significant effects.[18,19] Community-based supplementation programmes have varied in their impact on morbidity.[30,31] A community-based supplementation study in Ghana found a pronounced effect on severity of illness, and decreased utilisation of health services by children receiving vitamin A supplements.[32] Stansfield *et al.*,[33] however, found that children receiving supplements had a higher incidence of illness than controls. The methods and results of the latter study have, however, been questioned.[34-36]

In the light of our results, which indicate the importance of multiple risk factors for ARI, our support would be for a comprehensive approach to the improvement of vitamin A status of children in the community by addressing overall nutritional status and living conditions. This is, however, a long-term intervention strategy. In the short term, the study supports the role of vitamin A supplementation for at-risk groups. This strategy should be reviewed when the body of evidence indicates that vitamin A supplementation of all children has clear benefits that outweigh the opportunity costs.

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