

# Serum retinol concentrations and *Schistosoma mansoni*, intestinal helminths, and malarial parasitemia: a cross-sectional study in Kenyan preschool and primary school children<sup>1-3</sup>

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**ABSTRACT** Parasitic determinants of serum retinol concentrations were studied in 159 preschool (0.25–5.1 y) and 695 primary school (9.2–17 y) children in western Kenya. Mean serum retinol was 0.63  $\mu\text{mol/L}$  in preschool and 0.94  $\mu\text{mol/L}$  in primary school children; 62% and 24%, respectively, had serum retinol < 0.70  $\mu\text{mol/L}$ . Serum retinol was lower in boys than in girls among both preschool ( $P = 0.04$ ) and primary school children ( $P = 0.0001$ ). *Schistosoma mansoni*, *Ascaris lumbricoides*, hookworm, and *Trichuris trichiura* egg output and malarial parasitemia were determined and their relation with serum retinol assessed. Among preschool children, sex, elevated serum concentrations of C-reactive protein, and malarial parasitemia were significant predictors of serum retinol. Among the 63 children from whom stool samples were available, none of the helminth infections were significant predictors of serum retinol. For primary school children, age, sex, and *S. mansoni* egg output were predictors of serum retinol. Malarial parasitemia among nonimmune preschool children may contribute to low serum retinol, whereas malarial parasitemia did not have any effects in semiimmune primary school children. In contrast, the inverse relation between *S. mansoni* and serum retinol found in primary school children could be due to an effect of infection on serum retinol or an increased susceptibility to infection among children with low serum retinol. Although parasitic infections may contribute to poor vitamin A status in children, they do not explain the age and sex differences. *Am J Clin Nutr* 1997;66:665–71.

## INTRODUCTION

Vitamin A deficiency is an important cause of blindness in children, but even mild or subclinical vitamin A deficiency causes impaired immune function (1) and increased risk of mortality from infectious diseases (2, 3). Inadequate dietary intake of vitamin A is indisputably the major cause of vitamin A deficiency among children. However, high incidences of infectious diseases also contribute to deficiency because infections can lead to reduced intake and absorption of vitamin A, as well as to increased utilization in tissues and increased renal excretion of vitamin A (1).

Parasitic infections are prevalent in children in countries where marginal or low dietary intakes of vitamin A are widespread. In addition to the morbidity and mortality directly

attributable to these infections, unfavorable effects on host vitamin A status could be of public health importance. Furthermore, poor vitamin A status could increase susceptibility to parasitic infections, thus establishing a vicious circle. However, studies on interactions between vitamin A and infection are impeded by the lack of a satisfactory measure of vitamin A status (4). Serum concentrations of retinol are most often used, although these concentrations are homeostatically controlled over a wide range of liver concentrations of retinol. Additionally, serum retinol declines during the acute phase response to infections (5). It has therefore been recommended to measure the serum concentration of an acute phase protein in field studies in populations with high burdens of infectious diseases to control for potential confounding effects (6).

Malaria is holoendemic and *Schistosoma mansoni*, hookworm (*Necator americanus*), *Trichuris trichiura*, and *Ascaris lumbricoides* infections are prevalent in western Kenya and vitamin A status is generally poor. We conducted a cross-sectional study in 159 preschool and 695 primary school children to identify determinants of serum retinol. In particular, the relations between individual parasites and serum retinol were assessed by using multivariate analyses while controlling for the acute phase response and other potential confounding factors.

## SUBJECTS AND METHODS

### Subjects

The study was conducted in the Siaya District of the Nyanza Province in western Kenya. Residents of the study area are

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members of the Luo community; their principal occupations are subsistence crop farming, raising Zebu cattle, commercial fishing, and petty trade. Malaria is holoendemic in the study area; intestinal helminths and *S. mansoni* were prevalent whereas *S. haematobium* was not endemic. Primary school children were recruited from grades 5 and 6 in 19 primary schools in the study area. Preschool children consisted of all children enrolled in five preschools and their siblings. The preschools were attached to 5 of the 19 primary schools from which primary school children were included. All preschool children were accompanied by their mothers.

Blood samples were collected and serum retinol concentrations determined from 159 preschool children and 695 primary school children. The children were also examined for xerophthalmia. Additionally, questionnaire data and anthropometric measurements were obtained on the day of blood sampling. A thin and a thick blood slide were prepared from all children, and stool samples were collected on different days. Children with suspected clinical malaria received initial treatment, were referred for more definitive management and follow-up, and were excluded from the study.

Permission to conduct the study was obtained from the Kenya Medical Research Institute and National Ethical Review Committee and the Ministry of Health. The children and their parents were given information about the study, and the parents gave their written consent. The study was also approved by the Danish Central Medical Ethics Committee.

### Anthropometry

Height and weight were measured with the children barefoot and wearing light standard clothing. Height was measured to the nearest 0.5 cm and weight to the nearest 0.1 kg. A scale-stadiometer (Seca, Hamburg, Germany) was used for both height and weight measurements in primary school children and for weight measurements in preschool children. The length of preschool children was measured with a length board. Height and weight were related to references as SD scores ( $z$  scores). Height-for-age, weight-for-age, and weight-for-height  $z$  scores were computed using the nutritional anthropometry module of EPI INFO version 5 software (7) on the basis of National Center for Health Statistics–World Health Organization (NCHS-WHO) growth reference curves (8). The NCHS-WHO reference material is based on the length of children aged < 24 mo and the standing height of children aged > 24 mo. Because the length of children between 24 and 36 mo is 2 cm greater than the height, we subtracted 2 cm from the length of all preschool children aged > 24 mo before computing the  $z$  scores. Because reference data for weight-for-height were available only for boys < 11.5 y of age and < 145 cm tall and girls < 10.0 y of age and < 137 cm tall, this index could be computed only for preschool children.

### Serum retinol

Serum was prepared from blood samples taken from the antecubital veins between 0900 and 1300 and kept frozen at  $-20^{\circ}\text{C}$  for < 3 mo. Serum concentrations of retinol were measured by HPLC (Hitachi, Ltd, Tokyo) as previously described (9, 10). Before starting the extract procedure, 5  $\mu\text{L}$  retinyl acetate (100 mg/L) was added to 100  $\mu\text{L}$  serum as an internal standard. The extract was reconstituted with 100  $\mu\text{L}$

mobile phase (methanol:water, 95:5, by vol) and 20  $\mu\text{L}$  was injected into a guard-fitted, normal-phase stainless steel column (Microbondapak C18,  $3.9 \times 300$  mm, particle size 10  $\mu\text{m}$ ; Waters Associates, Milford, MA). The interbatch CV was 6.2%. The cutoff of  $\leq 0.70$   $\mu\text{mol/L}$  was used to indicate low vitamin A status (11).

### Indicators of acute phase response

In preschool children serum concentrations of C-reactive protein (CRP) were measured and used as an indicator of infection. Serum CRP was measured by an immunoturbidimetric reaction by using antiserum from Roche (Hoffmann-La Roche, Basel, Switzerland) and an automated analyzer (COBAS Mira, Hoffmann-La Roche). The standard curve was based on serially diluted CRP standard provided by the manufacturer. CRP T control (Hoffmann-La Roche) with an assigned value of 25.5 mg/L was used for internal quality control. The CV was 2.9%. Values > 5 mg/L were detectable and considered to be elevated and as such were used as an indicator of acute phase response.

In primary school children, questionnaire morbidity data, elevated body temperature, and elevated neutrophil count were used as indicators of infection. Structured interview data on fever, malaria, and diarrhea within the preceding 2 wk were used as clinical indicators of infection. Children rarely reported fever because fever was apparently perceived as malaria or headache. Sublingual temperatures were taken with a digital thermometer (Becton Dickinson, Franklin Lakes, NJ) and elevated body temperature was defined as a value >  $37.0^{\circ}\text{C}$ . Total white blood cell (WBC) counts were determined with an electronic counter (M530; Coulter Electronics, Ltd, Miami) and differential WBC counts were determined with conventional manual methods. Because total neutrophil counts were constant over age in primary school children, the 87.5 percentile corresponding to  $3.5 \times 10^9$  cells/L was arbitrarily chosen as the cutoff between normal and elevated neutrophil counts.

### Parasitology

Stool samples were collected on different days around the time of blood sampling and examined quantitatively for intestinal helminths and schistosome eggs. Duplicate 50-mg fecal thick smears covered with cellophane soaked in glycerine (12) were prepared from each of two to three stool samples. The smears were examined for hookworm eggs within 1 h and for eggs of *S. mansoni*, *T. trichiura*, and *A. lumbricoides* after  $\geq 24$  h clearing. The egg output was expressed as the mean number of eggs/g feces. From all children a thick blood slide was examined for malarial parasites. The number of parasites per 200 WBCs was counted. If there were < 10 parasites per 200 WBCs, 500 WBCs were examined. The number of malarial parasites per  $\mu\text{L}$  blood was computed on the basis of the total WBC count.

### Statistical analysis

According to Wilk-Shapiro rankit plots (STATISTIX VERSION 4.0; Analytic Software, Tallahassee, FL), serum retinol concentrations conformed to normality. The two-sample  $t$  test could therefore be used to test for differences in means between groups, and the chi-square test was used to test for differences in proportions. To identify predictors of serum retinol and

estimate their effects, multiple-linear-regression analysis with a backward elimination strategy was used, with age, sex, indicators of acute phase response, and parasitic infections as independent variables. Data on malarial parasitemia, *S. mansoni*, and intestinal helminth egg output were transformed by using a  $\log_{10}(x + 1)$  transformation. The level of significance used was 0.05. Residual analysis was performed by plotting standardized residuals against predicted values.

## RESULTS

The 159 preschool children (78 girls and 81 boys) were between 3 mo and 5 y of age. The 695 primary school children (360 girls and 335 boys) were between 9 and 17 y of age. Mean weight-for-age, height-for-age, and weight-for-height *z* scores are given in **Table 1**. The prevalences and intensities of parasitic infections are shown in **Table 2**. Stool samples, and hence data on schistosome and helminth infections, were available from all primary school children, but from only 63 (40%) preschool children.

### Serum retinol concentrations in preschool children

None of the preschool children had xerophthalmia (X1A or X1B) on clinical examination. The mean serum retinol concentration of all preschool children was 0.63  $\mu\text{mol/L}$  (95% CI: 0.60, 0.66) (**Table 3**), with 62.2% having serum retinol concentrations  $\leq 0.70 \mu\text{mol/L}$  and 5.0%  $< 0.35 \mu\text{mol/L}$ . According to bivariate analyses, serum retinol was significantly lower in the 28.2% of preschool children with elevated serum CRP compared with those with normal serum CRP (0.51 compared with 0.67  $\mu\text{mol/L}$ ,  $P = 0.0001$ ).

As shown in **Table 4**, sex, elevated serum CRP, and malarial parasitemia but not age were significant predictors of serum retinol in multiple-regression analysis, with an adjusted  $R^2$  of 0.13. The regression coefficient of sex corresponded to a 0.07- $\mu\text{mol/L}$  lower mean serum retinol concentration in boys than in girls. The estimated effect of malarial parasitemia was  $-0.02$  with sex and elevated serum CRP in the model. This corresponded to a 0.02- $\mu\text{mol/L}$  decline in serum retinol per log increase in intensity of infection expressed as parasites/ $\mu\text{L}$  blood. If elevated serum CRP was excluded from the model, the regression coefficient of malarial parasitemia changed to  $-0.04$  (95% CI:  $-0.06$ ,  $-0.02$ ;  $P = 0.0004$ ). If malarial parasitemia was included as a binary variable, the effect corresponded to a 0.10- $\mu\text{mol/L}$  lower serum retinol concentration

**TABLE 1**

Age, sex, and anthropometric *z* scores in preschool and primary school children

	Preschool children ( <i>n</i> = 159)	Primary school children ( <i>n</i> = 695)
Age (y) <sup>1</sup>	3.4 (0.25–5.1)	13.2 (9.2–17.0)
Sex ratio (female:male)	0.96	1.07
Weight-for-age <i>z</i> <sup>2</sup>	-0.69 (-0.87, -0.51)	-1.25 (-1.31, -1.19)
Height-for-age <i>z</i> <sup>2</sup>	-0.94 (-1.20, -0.69)	-1.15 (-1.23, -1.06)
Weight-for-height <i>z</i> <sup>3</sup>	-0.17 (-0.34, 0.00)	—

<sup>1</sup>  $\bar{x}$ ; range in parentheses.

<sup>2</sup>  $\bar{x}$ ; 95% CI in parentheses.

<sup>3</sup>  $\bar{x}$ ; 95% CI in parentheses. Not computable for primary school children.

**TABLE 2**

Prevalence and intensity of malaria and *Schistosoma mansoni* and intestinal helminth infections

	Preschool children ( <i>n</i> = 159) <sup>1</sup>		Primary school children ( <i>n</i> = 660)	
	Prevalence	Intensity	Prevalence	Intensity
Malarial parasitemia	70	1420 <sup>2</sup>	60	490 <sup>3</sup>
<i>S. mansoni</i>	27	204	72	77
Hookworm	21	20	55	57
<i>Trichuris trichiura</i>	37	185	46	43
<i>Ascaris lumbricoides</i>	13	11 240	15	2546

<sup>1</sup> 63 (40%) of the 159 preschool children were examined for helminth infections.

<sup>2</sup> Median eggs per gram feces in infected children except for malarial parasitemia.

<sup>3</sup> Intensity expressed as median malaria parasites per  $\mu\text{L}$  blood in infected children.

(95% CI: 0.03, 0.17;  $P = 0.005$ ) in the 71% of preschool children with parasitemia than in children without parasitemia. No confounding effect of age was seen. The potential effects of *S. mansoni* and intestinal helminths were assessed in a separate analysis because stool samples from only 40% of the preschool children were examined. None of these infections were predictors of serum retinol.

### Serum retinol concentrations in primary school children

In primary school children, the mean serum retinol concentration was 0.94  $\mu\text{mol/L}$  (95% CI: 0.91, 0.96), with 23.5% having low serum retinol concentrations (**Table 3**). None of the children had xerophthalmia (X1A or X1B). Based on bivariate analyses, serum retinol was lower in the 9.3% of primary school children with elevated neutrophil counts (0.84 compared with 0.95  $\mu\text{mol/L}$ ,  $P = 0.03$ ) and in the 24.6% with elevated temperatures (0.88 compared with 0.95  $\mu\text{mol/L}$ ,  $P = 0.04$ ). In contrast, there were no differences in serum retinol between those reporting diarrhea, malaria, or headache within the previous 2 wk compared with those not reporting these symptoms.

Results of backward multiple-regression analyses of serum retinol on age, sex, elevated temperature, elevated neutrophil count, malarial parasitemia, and *S. mansoni* and intestinal helminth egg output are shown in **Table 5**. Age, sex, and *S. mansoni* infection were significant predictors of serum retinol, whereas neither indicators of infection nor other infections remained in the model. The adjusted  $R^2$  was 0.10. The regression coefficient of age can be interpreted as a 0.05- $\mu\text{mol/L}$  increase in mean serum retinol per year increase in age. Additionally, serum retinol was 0.12  $\mu\text{mol/L}$  lower in boys than in girls. The increase with age was similar for boys and girls (0.04 compared with 0.05, respectively,  $P = 0.25$ ).

The estimated effect of *S. mansoni* egg output on serum retinol, corresponding to a 0.07- $\mu\text{mol/L}$  reduction per log increase in egg output (ie, from 1–10, 11–100, and 101–1000 eggs/g feces, etc), did not change if elevated temperature was forced into the model. Neither age nor sex was a confounder because the regression coefficient changed only to  $-0.06$  when these variables were excluded from the model. In contrast, neither malaria, *A. lumbricoides*, hookworm, nor *T. trichiura*

TABLE 3

Serum concentrations of retinol and prevalence of low values for boys and girls in preschool and primary school

	All	Girls	Boys	P <sup>1</sup>
Preschool (n = 78 girls, 81 boys)				
Serum retinol (μmol/L)	0.63 ± 0.21 <sup>2</sup>	0.67 ± 0.21	0.60 ± 0.21	0.04
Low (%) <sup>3</sup>	62.2 (99/159)	55.2	69.1	0.44
Primary school (n = 360 girls, 335 boys)				
Serum retinol (μmol/L)	0.94 ± 0.35	0.98 ± 0.36	0.88 ± 0.33	0.0001
Low (%) <sup>3</sup>	23.5 (163/695)	17.5	29.9	0.003

<sup>1</sup> P value for difference between boys and girls.<sup>2</sup>  $\bar{x} \pm SD$ .<sup>3</sup> Serum retinol  $\leq 0.70$  μmol/L.

remained in the model. For example, if *A. lumbricoides* egg output was forced into the model the regression coefficient was  $-0.004$  (95% CI:  $-0.03, 0.02$ ;  $P = 0.72$ ).

## DISCUSSION

Almost two-thirds of preschool and one-fourth of primary school children had low serum retinol concentrations. In both age groups boys had lower serum retinol concentrations than did girls. Serum retinol increased significantly with age in primary school children but not in preschool children.

### Infections

Both elevated temperature and elevated neutrophil count, but not reported illness, within the previous 2 wk were associated with reduced serum retinol in primary school children in bivariate but not multivariate analyses. For preschool children, elevated serum CRP was associated with low serum retinol. The decline in serum retinol during the acute phase response to infections is well known (4–6) and is probably caused by retinol being bound to the negative acute phase proteins retinol binding protein and transthyretin (13). The serum concentrations of these proteins fall as endothelial permeability increases to allow an increased flux into the extracellular space (13). This could be a cause of misclassification of vitamin A status if serum retinol is used as a measure of vitamin A status. However, the phenomenon is likely to be followed by increased utilization of vitamin A in tissues and accompanied by loss of vitamin A in urine (14), in which case the decline in serum retinol may reflect a reduction in liver reserves of vitamin A. Background infections in the study population eliciting an

acute phase response may therefore be potential confounding factors that should be controlled for in the analysis (6). In contrast, if the infection of interest exerts its effect on serum retinol through the acute phase response, then it should not be controlled for because the effect may vanish.

Infections may cause reduced intake and absorption of vitamin A as well as increased utilization in tissues and increased renal loss (1). Increased requirements for vitamin A in populations with a high burden of infection may be detrimental if dietary intake is marginal, thus making liver reserves of vitamin A low. The potential relation between parasitic infections, eg, malaria, *S. mansoni*, and intestinal helminths, and vitamin A status is not clear. Because many children in developing countries are continuously exposed to these parasites from early childhood, any effect on vitamin A status could be pivotal. Vitamin A deficiency could also increase susceptibility to parasitic infections. Such a synergistic two-way interaction between vitamin A deficiency and parasitic infections offers an explanation of the phenomenon of aggregation of helminths, ie, the finding of few worms in most children and heavy worm burdens in a few children.

### *S. mansoni* infection

The significant inverse relation between *S. mansoni* infection and serum retinol concentrations in primary school children was surprising, especially because of the absence of effect of other parasitic infections on serum retinol. Several cross-sectional studies have implied a negative effect of *S. mansoni* infection on serum retinol. In a hospital-based study from Egypt, significantly lower serum retinol concentrations were found in patients with *S. mansoni* infection than in healthy control subjects. Furthermore, among the patients, serum reti-

TABLE 4

Regression coefficients ( $\beta$ ) and corresponding P values of variables found to be significant predictors of serum retinol concentration in preschool children<sup>1</sup>

Variables	$\beta$	P
	$\mu\text{mol/L}$	
Sex <sup>2</sup>	$-0.07 (-0.2, -0.01)^3$	0.03
Serum CRP <sup>4</sup>	$-0.13 (-0.2, -0.05)$	0.002
Malaria parasitemia <sup>5</sup>	$-0.02 (-0.05, -0.003)$	0.03

<sup>1</sup> n = 159. Adjusted  $R^2 = 0.13$ .<sup>2</sup> Sex coded as 0 = girls and 1 = boys.<sup>3</sup> 95% CI in parentheses.<sup>4</sup> Serum C-reactive protein coded as 0 = normal and 1 = elevated.<sup>5</sup> Malaria parasites per  $\mu\text{L}$  blood transformed as  $\log_{10}(x + 1)$ .

TABLE 5

Regression coefficients ( $\beta$ ) and corresponding P values of variables found to be significant predictors of serum retinol concentration in primary school children<sup>1</sup>

Variables	$\beta$	P
	$\mu\text{mol/L}$	
Age in years	$0.05 (0.03, 0.06)^2$	$6 \times 10^{-10}$
Sex <sup>3</sup>	$-0.12 (-0.17, -0.07)$	$2 \times 10^{-6}$
<i>Schistosoma mansoni</i> egg output <sup>4</sup>	$-0.07 (-0.09, -0.04)$	$2 \times 10^{-8}$

<sup>1</sup> n = 695. Adjusted  $R^2 = 0.10$ .<sup>2</sup> 95% CI in parentheses.<sup>3</sup> Sex coded as 0 = girls and 1 = boys.<sup>4</sup> Eggs per gram feces (epg) transformed as  $\log_{10}(\text{epg} + 1)$ .

nol was lower in those with schistosomal polyposis and hepato-splenic disease than in those with uncomplicated infection (15). A community-based study from Liberia reported lower serum retinol concentrations in children and adults with *S. mansoni* infection than in those without helminth infections (16). Obviously, the reported associations may be due to confounding factors not controlled for in these studies. Age is such a potential confounding factor, because both serum retinol concentrations and schistosomiasis often depend on age. Additionally, if other infections giving rise to an acute phase response are associated with *S. mansoni* infection, a spurious association between *S. mansoni* and low serum retinol will appear. We previously reported an association between *S. mansoni* and low serum retinol in a cross-sectional study in Zimbabwe in which age and acute phase response were controlled for by using multivariate-regression analysis (17). The data presented here confirm this finding, and the estimated effect of *S. mansoni* of a 0.07- $\mu\text{mol/L}$  reduction in serum retinol per log increase in eggs/g feces was similar to the 0.03- $\mu\text{mol/L}$  reduction per increase in egg output of 100 eggs/g feces reported from Zimbabwe.

Although cross-sectional studies do not allow inferences to be drawn about causality and direction of cause and effect, previous studies interpreted the association as being due to an effect of the infection on serum retinol. Although this may be the case, there are no data to support this, and we recently failed to show any effect of *S. japonicum* infection on liver retinol concentration in pigs (unpublished data, 1996), which are considered to be a good model of not only *S. japonicum* (18) but also *S. mansoni* infection in humans. The association could also be due to an increased susceptibility to *S. mansoni* infection in persons with low serum retinol concentrations. In fact, studies in the *S. mansoni* rat model showed that vitamin A deficiency leads to reduced humoral immune response to schistosome antigens (19) and increased worm burdens (20). Thus, the two-way interactions between *S. mansoni* and vitamin A should be studied in randomized controlled trials.

### Ascariasis

No relation between ascaris infection and low serum retinol was seen in our study. Several studies showed impaired vitamin A absorption in children and adults (21–23) with *A. lumbricoides* infection, which was occasionally reversible with treatment (21, 22), whereas other studies failed to detect any effects (24). However, neither of the studies found a correlation between intensity of infection and degree of malabsorption (21, 22). Associations between ascaris infection and low serum retinol were found in preschool children in Panama (25) and Nepal (26) and in Indonesian preschool children in whom the low serum retinol concentrations were reversible after deworming (27). In contrast, another study of young children in Indonesia found no effect of deworming on serum retinol or modified-relative-dose-response test (28).

### Malaria

Malarial parasitemia was a significant predictor of serum retinol in preschool but not primary school children. Although the effect was seen even if the acute phase response was controlled for, the estimated effect was higher if elevated serum CRP was excluded from the analysis.

Low serum retinol concentrations during malaria attacks have been reported in children (29–31) and adults with uncomplicated (5) and severe (32) malaria. The decline in serum retinol during clinical malaria in Gambian (30) and Indian (31) children was considered to be merely a metabolic adjustment to the infection and not reflective of reduced liver stores of vitamin A. However, the larger decline in serum concentration of provitamin A compared with non-provitamin A carotenoids seen in Thai patients was interpreted as reflecting increased utilization of vitamin A during malaria (5).

In a study in children in Tanzania, serum retinol concentrations were inversely correlated with malarial parasitemia (33). However, this could have been due to confounding by age as suggested by the authors. Similarly, in our analysis the effect of malarial parasitemia and not clinical malaria was examined, but in contrast, age as well as the acute phase response were controlled for. In nonimmune preschool children, malarial parasitemia is associated with repeated attacks of clinical malaria. It is likely that the flux of the retinol-retinol binding protein complex to the extravascular space that takes place during these repeated attacks of malaria is followed by increased tissue utilization (5) and renal loss of vitamin A (14). In contrast, because malaria transmission was epidemiologically stable in our study area, primary school children were less vulnerable as a result of acquired immunity. Our finding of an effect of malarial parasitemia on serum retinol concentrations in children aged < 5 y but not in older children could be explained by the stable transmission pattern in the study area. Furthermore, this differential effect is in line with the early finding of McGregor et al (34) that malaria was detrimental to the growth of young children but not older children.

Although vitamin A-deficient rats have been shown to be more susceptible to infection and disease when exposed to *Plasmodium berghei* (35), there is no evidence that poor vitamin A status increases morbidity from malaria in humans (36). Again, because we found an association between malarial parasitemia and low serum retinol concentrations in only preschool and not primary school children, the association is most likely due to an effect of previous clinical malaria, which is more common in young children, on serum retinol. Thus, we believe that malarial parasitemia contributes to low serum retinol through the effects of the acute phase response.

If the acute phase response in the study population originates from infections other than malaria, it should be controlled for because it is confounding the estimated effect of malarial parasitemia on serum retinol. In contrast, if the acute phase response is due to malaria and is mediating the effect on vitamin A status, it should not be controlled for. However, if the decline in serum retinol during the acute phase response is partially transient, ie, not all of the retinol leaking into the extravascular space is being utilized, the effect of malarial parasitemia will be underestimated if the acute phase response is controlled for. Accordingly, the effect of malarial parasitemia probably corresponds to a decline in serum retinol of between 0.02 and 0.04  $\mu\text{mol/L}$  per log increase in malarial parasites/ $\mu\text{L}$  blood. Thus, the mean serum retinol concentration in children with 10 000 malarial parasites per  $\mu\text{L}$  blood will be 0.08 to 0.16  $\mu\text{mol/L}$  lower than the concentration in uninfected children. Malaria



is likely to contribute to vitamin A deficiency in nonimmune populations with marginal dietary intakes.

### Conclusion

The age and sex differences in serum retinol were not explained by differences in infectious disease burden, as these effects remained when indicators of infections and parasitic infections were controlled for in the analyses. Although lower serum retinol in boys than in girls has been found even in newborn babies (37), possible cultural factors responsible for differences in dietary intake of preformed vitamin A and provitamin A should be explored because they may provide the key to improving the vitamin A status of children in developing countries. A recent study from southwestern Kenya concluded that increases in household income do not necessarily result in improved vitamin A intake, but that other health, sanitation, and nutrition interventions are needed (38). These could be combined school-based interventions aimed at controlling parasitic infections and improving vitamin A status. It is therefore essential that the nature of the two-way interactions between vitamin A deficiency and *S. mansoni*, malaria, and other infections be established in randomized controlled intervention trials. ■

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