Articles

Vitamin A supplementation in northern Ghana: effects on clinic attendances, hospital admissions, and child mortality

*Ghana VAST Study Team**

Summary

Although most studies on the effect of vitamin A supplementation have reported reductions in childhood mortality, the effects on morbidity are less clear. We have carried out two double-blind, randomised, placebo-controlled trials of vitamin A supplementation in adjacent populations in northern Ghana to assess the impact on childhood morbidity and mortality.

The Survival Study included 21 906 children aged 6–90 months in 185 geographical clusters, who were followed for up to 26 months. The Health Study included 1455 children aged 6–59 months, who were monitored weekly for a year. Children were randomly assigned either 200 000 IU retinol equivalent (100 000 IU under 12 months) or placebo every 4 months; randomisation was by individual in the Health Study and by cluster in the Survival Study. There were no significant differences in the Health Study between the vitamin A and placebo groups in the prevalence of diarrhoea or acute respiratory infections; of the symptoms and conditions specifically asked about, only vomiting and anorexia were significantly less frequent in the supplemented children. Vitamin-A-supplemented children had significantly fewer attendances at clinics (rate ratio 0·88 [95% CI 0·81–0·95], p=0·001), hospital admissions (0·62 [0·42–0·93], p=0·02), and deaths (0·81 [0·68–0·98], p=0·03) than children who received placebo. The extent of the effect on morbidity and mortality did not vary significantly with age or sex. However, the mortality rate due to acute gastroenteritis was lower in vitamin-A-supplemented than in placebo clusters (0·66 [0·47–0·92], p=0·02); mortality rates for all other causes except acute lower respiratory infections and malaria were also lower in vitamin A clusters, but not significantly so.

Improving the vitamin A intake of young children in populations where xerophthalmia exists, even at relatively low prevalence, should be a high priority for health and agricultural services in Africa and elsewhere.

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Introduction

An association between vitamin A deficiency and an increased risk of childhood morbidity[1–4] and mortality[5] has been reported in observational studies, and intervention trials in Asia have reported reductions in mortality ranging from 6% to 54%.[6–11] By contrast, a study in Sudan reported a small increase in overall mortality.[12] In the three studies that reported large reductions in mortality and listed causes of death, mortality rates for diarrhoea and measles fell but the rate for acute respiratory infections (ARI) did not change.[8–10] Two of three studies reporting on morbidity and mortality found no effect on the prevalence of any illness studied despite substantial falls in mortality[6,8,13,14] (the other reported no significant effect on morbidity or mortality[11]). Clinical trials have shown that treatment with vitamin A reduces the severity of illness and mortality in children with measles,[15–17] even in areas where eye signs of vitamin A deficiency are rare.

We have carried out two randomised, double-blind, placebo-controlled trials to assess the effect of 4-monthly large doses of vitamin A on childhood mortality (the Ghana Vitamin A Supplementation Trials [VAST] Survival Study) and morbidity (the VAST Health Study) in northern Ghana.

Subjects and methods

The trials took place in the guinea savannah area of Ghana in the Kassena-Nankana District, on the border with Burkina Faso (figure 1). The area has a sub-Sahelian climate, and the mean annual rainfall was 852 mm during 1981 to 1990, with 90% of the rain falling between April and September.[18]

The study populations were exclusively rural. Extended families live in a group of houses (a compound) connected by a single outer wall, and surrounded by their farmland. The main staple foods are millet, sorghum, and groundnuts, and the diet is deficient in carotenoids and vitamin A. Red palm oil, a major source of carotenoids in coastal West Africa, was found in only 2% of compounds during baseline surveys. However, about a third of compounds owned at least one mango tree, and about 10% one or more pawpaw (papaya) trees. Vitamin A deficiency and xerophthalmia are recognised as problems locally; words exist for night blindness in all the local languages and cases of xerophthalmia are reported by local ophthalmological services. There was no vitamin A supplementation programme within the study area.

The district is underserved by health services; one hospital and three health centres, with limited outreach services, serve about 180 000 people. Immunisation coverage and access to other maternal and child health services are correspondingly low.

All compounds in the study areas were included in the trials. They were listed and marked on specially prepared maps (1/5000 scale) and a full census of all residents was carried out shortly before the start of each trial. All children living in compounds within the

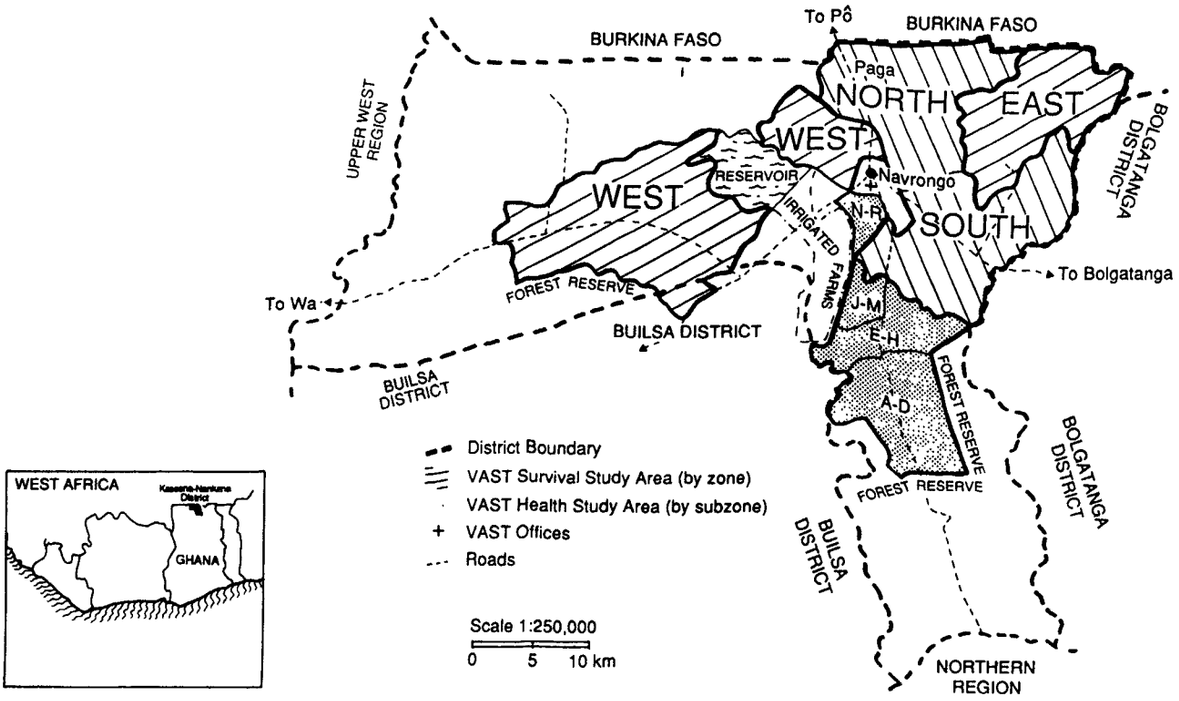

Figure 1: **Kassena-Nankana district**

study areas were eligible to enter the trials at any of the 4-monthly dosing points, once they had reached the age of 6 months. Children born from 1984 onwards were included in the Survival Study, but the Health Study restricted admission to children born from 1986 onwards. The Survival Study trial was carried out between September, 1989, and December, 1991, and the Health Study trial between June, 1990, and August, 1991.

At enrolment, the dates of birth of the children and their mothers were assessed by means of detailed local events calendars, supplemented by any written documentation available. Other information collected included an illness history, vaccination history, and anthropometric measurements on the child, the survival status of siblings, parental education, and mother's age. For each compound, data were collected on the type of house, possessions, animals, and access to vitamin-A-rich foods.

At the start of each trial, blood samples were collected to establish baseline serum retinol concentrations. In the Health Study, all children had serum retinol measurements at baseline and then a different, randomly chosen one-third sample was tested at each of the three subsequent dosing rounds. In the Survival Study, a random, stratified sample of 520 compounds was selected and blood samples were taken from all the children living in these compounds at baseline and at the end of the trial.

A fingerprick blood sample was taken into a 1 mL amber microtube with serum separator gel (Becton Dickinson, Oxford, UK). Samples were stored on ice and centrifuged within 12 h. The serum was stored at −40°C in foil-covered tubes, then transported on dry ice to the Nutritional Biochemistry Laboratory in the Institute of Child Health in London, where the serum retinol content was measured by high-performance liquid chromatography (Spectraphysics, Hemel Hempstead, UK) with a 10 cm ODS2 column (Pharmacia, Milton Keynes, UK) and an ultraviolet detector (Phillips, Cambridge, UK).

The Survival Study area was divided into 185 geographical areas (clusters) based on boundaries such as roads, paths, or streams, with 30–77 compounds in a cluster (mean 51); the cluster was used as the unit of randomisation. Overall, 92 clusters were assigned vitamin A and 93 placebo treatment. In the Health Study, individual children were randomly assigned either vitamin A or placebo. Randomisation was blocked in both studies to ensure similar numbers of children in each group in each part of the study area. Randomisation was carried out in London by an independent statistician, who held the randomisation code and who also did an interim analysis of the mortality results from the Survival Study for the trial's data-monitoring committee after a year of follow-up.

Vitamin A and placebo were supplied by Hoffmann-La-Roche's Sight and Life Programme, and were similar in taste and colour. In the Survival Study, liquid vitamin A or placebo was supplied in opaque 150 mL bottles containing 20 IU/mL vitamin E alone (placebo) or plus 100 000 IU/mL retinol equivalent as retinyl palmitate (vitamin A) in purified peanut oil. Each bottle had a unique number, and was labelled with a cluster code before despatch to Ghana. In the Health Study, vitamin A and placebo were supplied in gelatin capsules, individually packaged in opaque envelopes labelled with one child's unique identification number. The capsules contained 200 000 IU retinol equivalent as retinyl palmitate (vitamin A) or peanut oil only (placebo).

Supplements were stored in sealed bottles at room temperature. Random samples of the vitamin A bottles and of the capsules were returned for testing of retinol content by Hoffmann-La-Roche's laboratories in Basel; there was less than 20% loss of potency, even in vitamin A stored for up to 2 years.

In both trials, at each dosing round, children aged less than 6 months were not eligible, children 6–11 months old received 100 000 IU retinol equivalent or placebo, and children 12 months or older were given 200 000 IU retinol equivalent or placebo. Vitamin A was given to all children during the final dosing round of each trial.

In the Survival Study, children were visited and dosed by trained fieldworkers every 4 months for 2 years in seven survey rounds. At each visit each child was recorded as being present, temporarily absent, moved away, or dead. A child was classified as being temporarily absent if he or she was not in the compound when visited at least three times during a week. The parents of children found to be suffering from any illness at a fieldworker's visit were advised to take them to the nearest health facility for diagnosis and treatment.

In the Health Study, morbidity surveillance was based on weekly home visits by fieldworkers. At each visit, a detailed interview was conducted about the occurrence on each day of the week of 21 listed symptoms, signs, and conditions, using locally defined terms where appropriate. Recall was aided by use of a pictorial daily health diary, on which mothers were taught to record that the child was healthy or to mark the occurrence of diarrhoea, cough, or any other illness. Further questions and observations were made to assess the severity of any diarrhoeal or respiratory illnesses reported (to be published elsewhere).

The Health Study area had no static health facility, but weekly mobile clinics were held, at which study children were offered a highly subsidised service. At their weekly visits, fieldworkers were

instructed to refer ill children to the clinics, according to specified criteria. All study children who attended the clinic were seen by a physician, who recorded the diagnoses and treatment. A standard, detailed clinical assessment was also carried out on a subsample of these children. Children presenting with acute respiratory infections were referred to the district hospital for chest radiography, and severely ill children were admitted to hospital, where they were treated by standard protocols, and monitored daily by the study physician. Direct admissions of study children to the district hospital were also notified to the physician for assessment, monitoring, and treatment by the same standard treatment protocols.

Children were screened for signs of xerophthalmia every 4 months. In the Survival Study, fieldworkers at their 4-monthly home visits screened children for suspected night blindness, Bitot's spot, or corneal abnormality, and referred affected children for further assessment by a study physician. In the Health Study, each child was examined every 4 months by a physician.

All children with confirmed active xerophthalmia or its sequelae (corneal scars) were withdrawn from the trial at diagnosis. They were given three large doses of vitamin A over a week, and received vitamin A in all subsequent survey rounds. Because of the frequent follow-up in the Health Study, we could detect and treat cases of measles with vitamin A. These children were also excluded from the trial from that point.

Child deaths were identified at the time of the home visits, and also through a network of about 100 key informants—members of the study community who were asked to record all pregnancies, births, and child deaths in their area. Information was collected from the informants every 2 weeks. Specially trained staff interviewed the parents or the nearest relative of any study child who died. They recorded information on the circumstances of the death and the symptoms and signs that preceded it on a form that included both an open history of the final illness and screening questions for the presence of common symptoms, followed by the application of appropriate modules with precoded answers. More than 90% of interviews were done within 7 months of the child's death (median interval 2·9 months).

Verbal autopsy questionnaires were examined independently by three physicians who assigned the cause of death to one of eleven categories, which included "miscellaneous" and "unknown". If at least two of the three physicians assigned the death to the same category, it was taken as the cause, otherwise the cause was classified as "unknown".

Several methods were used both to promote and to check on data quality. These included weekly visits to each fieldworker by a supervisor, who observed interviews, revisited compounds, and either conducted full re-interviews or checked a more limited set of information on a sample of recently completed interview forms. Meetings were held weekly between supervisors and headquarters field and data-processing staff, and at least once every 2 weeks between groups of fieldworkers and their supervisors to ensure good two-way communication. Both fieldworkers and supervisors received regular training courses.

Completed forms were checked manually by the supervisors, before independent data entry into computers by two clerks. After typing errors had been corrected, the data were checked for range and consistency. Any discrepancies that could not be resolved in the headquarters led to a revisit to the child's home and checking of information on the relevant variables.

Regular computer analyses of the results reported by each fieldworker were done to identify workers whose results differed substantially from those of their colleagues; they were given extra supervision and, where necessary, retraining.

All data entry and processing were done in the study headquarters in Navrongo with IBM PS/2 computers and dBase III+ software. Analyses were carried out in Navrongo and London with dBASE III+, Epi Info 5·00, SPSS PC+ 4·0, and GLIM 3·77. Two-tailed significance tests were used throughout, and continuity corrections applied where appropriate. Preliminary results were reported to the study communities, the district and regional health services, and the Ministry of Health of Ghana within 4 months of the end of data collection.

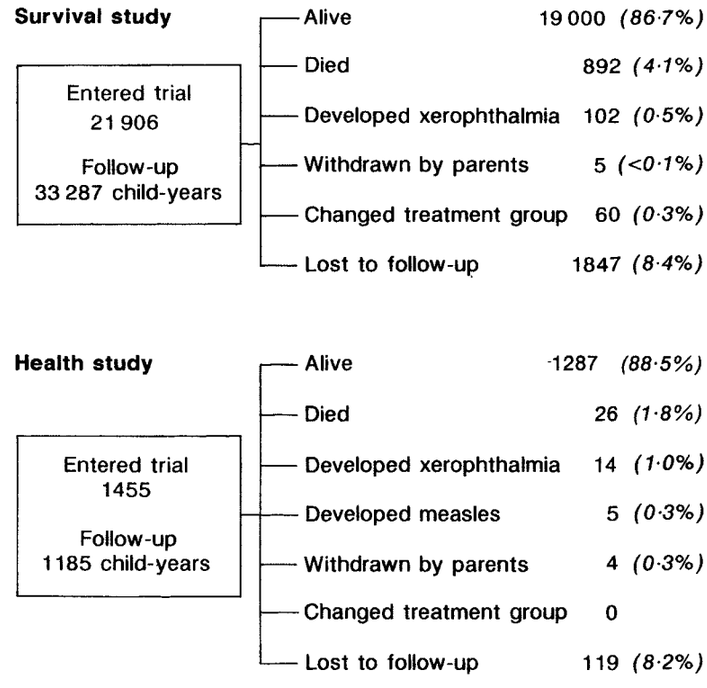

Figure 2: **Follow-up of study children**

Children who were at least 6 months old entered the trials at the first dosing round or at a subsequent round and left at the last dosing round, or when they moved out of the study area, died, or were withdrawn from the trial. Confirmed xerophthalmia cases were excluded from the date of diagnosis. In the Survival Study, children could move from one treatment group to the other by moving between clusters with different treatment assignments. Such children were excluded from the date they received their first dose of the different treatment.

Since children were randomised to treatment group by cluster in the Survival Study, the results, both of the baseline comparisons and the mortality rates, were analysed by a comparison of the mean of the results in each of the 92 vitamin A clusters against the mean of the results in each of the 93 placebo clusters. Each cluster's mortality rate was calculated by dividing the number of deaths by the child-years of follow-up. The ratio of the mean mortality rate in the vitamin A and placebo clusters was used to measure the mortality impact of vitamin A supplementation, with 95% CI calculated by the method of Armitage and Berry.[19]

An independent data-monitoring committee reviewed the mortality results from the first 12 months of follow-up in the Survival Study, and recommended the continuation of the trial to the end of the planned 24 months of follow-up. The results of this interim analysis were not revealed to the members of the study team until after the trial.

In comparing mean daily prevalence rates of morbidity between vitamin A and placebo groups in the Health Study, separate daily prevalence rates were calculated for each child for each of the intervals between dosing points. These were then averaged to give overall mean rates for each treatment group. The CIs for the rate ratios were calculated by means of a formula for determining the confidence interval of the ratio of two normal means.[19]

Ethical approval for both trials was obtained from the Ministry of Health of Ghana, and from the ethics committee of the London School of Hygiene and Tropical Medicine. The trials were explained in detail to all the local, regional, and district authorities and paramount chiefs, who gave their approval. Efforts were made to keep the communities informed of the studies' purposes, and of any new developments, through meetings open to all community members, and by announcements at market places. The trial was also explained and consent was sought from the head of each compound and the parents or guardians of each eligible child before enrolment.

Results

The prevalence of xerophthalmia at baseline was 0·7% in the Survival Study children and 1·5% in the Health Study children. In each study, the rates in the vitamin A and placebo groups were similar. The proportions of children with low baseline serum retinol concentrations were substantial in both trial populations. In the Survival Study, 14·4% were severely deficient (<0·35 μmol/L) and 42·5% moderately deficient (0·35–0·69 μmol/L); the equivalent rates were 15·8% and 57·6% among the Health Study children. The treatment groups were compared at baseline with respect to more than fifty characteristics. In both trial populations, the treatment groups were significantly different ($p<0·05$) for only two variables, which is the number expected by chance.

No parent refused permission for a child to enter the trials. Losses to follow-up were less than 10% in both trials (figure 2) and similar in the treatment groups.

The 21 906 children who entered the Survival Study were followed up for 33 287 child-years (16 508 vitamin A group, 16 779 placebo group). Dosing compliance was similar in the two groups; an average of 89·5% of eligible children were successfully treated in each round. The commonest reason for missing a dose was absence from home at the time of the fieldworker's visit. Dosing errors were rare (less than 0·7% of all doses given). Most were due to mislabelling of bottles.

1455 children entered the Health Study and were followed up for 1185 child-years (596 vitamin A group, 589 placebo group). Morbidity information was missing for 5·7% of the weekly follow-up visits owing to temporary absences of the study children or their mothers, but the missing data were equally distributed between the treatment groups. At each dosing point, an average of 94·7% of eligible children received the supplement or placebo.

Symptom/condition	Mean daily prevalence (%)		Prevalence ratio ‡	p
	Vitamin A	Placebo		
Specifically asked about				
Diarrhoea	15 5	15 9	0 98	0 55
Daytime cough	13·2	13·0	1·02	0 67
Blocked nose	11 5	11 3	1·01	0·82
"Tied ribs"*	1·1	1·1	0 98	0 86
Difficulty breathing	1 2	1·2	0·96	0 70
Rapid breathing	1 1	1 3	0·81	0 11
Ear pain	0·7	0 9	0·82	0·40
Ear discharge	0 7	0 8	0 91	0 72
Measles	0 1	0 1	1·10	0 79
Skin rash	5 0	4 8	1 04	0·61
Pua*	2 2	2·0	1 08	0 30
"Hot body"*	16 7	16 7	1 00	0·89
Vomiting	2 0	2·3	0 84	0 02
Refusing food/breastmilk	1 3	1 6	0 84	0 03
Reported but not asked about				
Skin ulcers/boils	1 3	1 6	0 84	0 13
Red/painful/discharging eyes	1 6	1 8	0 91	0·39
"Sore anus"*	0 8	0 9	0·93	0 62
Other†	1 6	1 8	0 91	0 29

* Locally defined symptoms: tied ribs = severe respiratory illness; Pua = febrile illness including symptoms of malaria; hot body = raised body temperature.
†Included convulsions, worms, headache, stomach pains.
‡Vitamin A/placebo.

Table 1: **Mean daily prevalence of symptoms/conditions in health study during follow-up**

	No of deaths (% of total)	No of deaths		Ratio of mean mortality rates† (95% CI)
		Vitamin A clusters (n=92)	Placebo clusters (n=93)	
Deaths with established cause*				
Acute gastroenteritis	180 (25 8%)	69	111	0 66 (0·47–0 92)
Malaria	161 (23·1%)	76	85	1·03 (0·74–1 43)
Measles	134 (19 2%)	61	73	0 82 (0·48–1·40)
Acute lower respiratory infection	92 (13·2%)	47	45	1 00 (0 61–1 64)
Chronic diarrhoea or malnutrition	58 (8 3%)	22	36	0 67 (0 38–1·18)
Injury	20 (2·9%)	10	10	0 85 (0 34–2 07)
Meningitis	11 (1 6%)	4	7	0 66 (0 18–2 49)
Other	41 (5·9%)	19	22	0 73 (0 38–1 41)
Cause not known	.	89	106	0·81 (0 59–1 13)
Total		397	495	0 81 (0·68–0·98)

*Total with established cause = 697. †Vitamin A/placebo.

Table 2: **Total and cause-specific mortality in Survival Study**

There were only two significant differences between the vitamin A and placebo groups in the mean daily prevalence of the symptoms/conditions investigated at the weekly visits in the Health Study (table 1)—prevalence of vomiting and refusal of food or breastmilk.

In the Health Study clinic attendance rates were significantly lower in the vitamin A group than in the placebo group (1193 *vs* 1341 attendances, rate ratio 0·88 [95% CI 0·81–0·95], $p<0·001$). A child in the vitamin A group was significantly less likely than a placebo-treated child to have made several clinic visits ($p=0·019$); for example children in the vitamin A group were 27% (95% CI 4–45%) less likely to have attended the clinic 3 or more times during a 4-month dosing interval. Similarly, hospital admission rates were significantly lower in the vitamin A group than in the placebo group (36 *vs* 57 admissions, rate ratio 0·62 [0·42–0·93], $p=0·02$). The rate ratio for admission was similar when only the first admission of each child was counted (27 *vs* 42, rate ratio 0·65 [0·41–1·04], $p=0·09$).

There were 892 deaths among the children in the Survival Study, which gave an overall mean mortality rate for all clusters of 27·1 per 1000 child-years of follow-up. 397 of the deaths were in vitamin A clusters (mean mortality rate 24·4 per 1000 child-years) and 495 in placebo clusters (29·9 per 1000 child-years). The ratio of the mean mortality rates was 0·81 (95% CI 0·68–0·98, $p=0·03$, table 2). The ratio of mean mortality rate was smaller in boys than in girls (0·73 [0·59–0·92] *vs* 0·90 [0·71–1·15]) but the difference was not significant ($p=0·3$). A protective effect of vitamin A was apparent in five of seven age groups, but there was no consistent trend in the size of the ratio by age.

A probable cause of death was established for 697 (78·1%) of the 892 deaths (table 2). The mortality rate due to acute gastroenteritis was significantly lower in the vitamin A clusters than in the placebo clusters. Mortality rates for all the other causes of death except acute lower respiratory infections and malaria were lower in the vitamin A group but none was significant at $p<0·05$, and, overall, the difference in the size of the effect of vitamin A supplementation by cause was not statistically significant.

There were 26 deaths among trial children in the Health Study, 6 in the vitamin-A-supplemented group and 20 in the placebo group.

Discussion

These trials broke new ground in several ways. The two trials were carried out in adjacent populations in West Africa; one looked in detail at the effect of vitamin A supplementation on morbidity and the other at its effect on mortality. We assessed the effect of vitamin A supplementation on the care sought for illness (clinic attendances and hospital admissions). The trials were carried out in a population with xerophthalmia rates that were very close to the threshold used by WHO to define a population as having a xerophthalmia problem of public health significance (1%);[20] previously reported studies were done in populations with substantially higher rates of xerophthalmia.

Our results may explain the puzzling results from at least two previous trials, which failed to find an impact on morbidity[13,14] even in the presence of a large effect on mortality.[6,8] Those studies collected data on a limited number of symptoms/conditions, without detailed information on their severity or the care-seeking provoked. We also found no effect on reported morbidity, though there was a suggestion that the prevalence of vomiting and refusal of food or breastmilk, both of which tend to be associated with severe episodes of illness, were lower in the supplemented children. However, we did find a strong influence on the occurrence of episodes severe enough to lead the mother to take the child to a clinic, and those that subsequently resulted in the child being admitted to hospital, as well as an effect on mortality. Thus, it seems that vitamin A supplementation reduced the frequency of severe and lethal illnesses without decreasing the frequency of less severe illnesses.

Vitamin A has two main effects on the immune system—enhancement of non-specific immunity by maintaining the physical and biological integrity of epithelial tissue as the first barrier to infection,[21-24] and increasing the effectiveness of the immune response to infection once the epithelial barrier has been breached.[25-27] The first should result in a lower incidence of infections, possibly in combination with decreased severity due to a lower average "dose" of pathogens crossing the mucosal barrier, whereas the second will tend towards a decreased severity, but not incidence of infection. The overall observed impact of supplementation will depend on the relative enhancement of these two components of the immune system in the population. Our results imply that the effects of vitamin A supplementation on the immune response to infection after the epithelial barrier has been breached are of greater functional significance than the effects on the integrity of the epithelial barrier itself.

The trials are the first to show an effect of prophylactic vitamin A supplementation on morbidity or mortality in Africa. The only other similar trial in Africa (in Sudan[12]) did not show an effect of vitamin A supplementation on child survival (relative risk = 1·06 [95% CI 0·82–1·37]). The investigators speculated that the lack of effect in their study population was due to the 6-monthly rather than 4-monthly dosing schedule, the low mortality rate in the control group, or the postulated lack of other nutrients, such as fat or zinc, in the diet.

Our findings of a 19% reduction in all-cause mortality with vitamin A supplementation and the substantial reductions in clinic attendance rates and hospital admissions are consistent with the results of five large trials in Asia,[6-10] and observational studies in Asia.[1-5] Only one trial in Asia did not find significantly lower child mortality with vitamin A supplementation;[11] however, even in that trial, the lower 95% confidence interval on the ratio of the mortality rates was below 0·81.

The all-cause mortality results of our trials are important for two reasons. Firstly, they showed that improving the vitamin A intake of at least some populations of young African children can substantially reduce their mortality. Secondly, this effect on all-cause mortality was in a population that had a vitamin A deficiency problem of marginal public health importance;[20] baseline xerophthalmia rates were substantially higher in the Asian trials.[6-11] Nonetheless, there was evidence that vitamin A supplementation reduced the incidence of xerophthalmia.

Our study found a rate ratio of 0·66 for acute gastroenteritis deaths and of 0·67 for deaths due to chronic diarrhoea, malnutrition, or both. A reduction of at least 30% in child mortality due to diarrhoeal diseases has now been found by all trials that have found a significant effect on overall mortality and have also examined causes of death.[8-10] By contrast, we found no reduction in deaths attributed to acute lower respiratory infections in the vitamin-A-supplemented group. The effect of vitamin A supplementation on such deaths has not been consistent in previous trials,[8-10,12] though none has found a significant change. Similarly, we found no reduction in deaths due to malaria. Malaria was probably a much more important immediate and underlying cause of death in this population than in any other trial population, with the possible exception of the Sudan, where "fever" was the second commonest symptom associated with death.[12] The other major cause of death in our trial was measles, in which the ratio of the mortality rates was 0·82, though this ratio did not significantly differ from 1·0.

The results of this study have important health policy implications. They show that improving the vitamin A intake of young children in areas where xerophthalmia exists, even at low prevalence, should be a high priority for both health and agricultural services. If routine interventions can be devised that effectively improve vitamin A status, the burden of xerophthalmia, other severe illness, and mortality in children will be substantially reduced. As well as these direct benefits to the population, there will be substantial indirect benefits owing to substantial reductions in clinic attendances and hospital admissions. Health services appropriate a significant proportion of national budgets, and the economic and social costs incurred by the family of an ill child are also large.

Since the impact of improvements in vitamin A status is likely to be related to the extent of deficiency in the population, there is an urgent need for surveys of the prevalence of vitamin A deficiency and xerophthalmia. Remarkably little is known about the extent of the problem in most countries in Africa, the Middle East, Asia, and Latin America. It will then be important to gather information on local dietary and agricultural practices and beliefs to assess the feasibility of improving the production, storage, and consumption of local vitamin-A-rich foods, the introduction of new foods, or fortification of a locally consumed food. Other potential strategies include the provision of vitamin A supplements to at-risk groups. Although likely to be the least cost-effective strategy for the improvement of vitamin A status in the long term, even this approach is a highly cost-effective child survival intervention.[28]

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References

1 Sommer A, Katz J, Tarwotjo I. Increased risk of respiratory disease and diarrhoea in children with pre-existing vitamin A deficiency. *Am J Clin Nutr* 1984; **40:** 1090–95.

2 Milton RC, Reddy V, Naidu AN. Mild vitamin A deficiency and childhood morbidity—an Indian experience. *Am J Clin Nutr* 1987; **46:** 827–29.

3 Bloem MW, Wedel M, Egger RJ, et al. Mild vitamin A deficiency and risk of respiratory tract diseases and diarrhea in preschool and school children in Northeastern Thailand. *Am J Epidemiol* 1990; **131:** 332–39.

4 El Bushra HE, Ash LR, Coulson AH, Neumann CG. Interrelationship between diarrhea and vitamin A deficiency: is vitamin A deficiency a risk factor for diarrhea? *Pediatr Infect Dis J* 1992; **11:** 380–84.

5 Sommer A, Tarwotjo I, Hussaini G, Susanto D. Increased mortality in children with mild vitamin A deficiency. *Lancet* 1983; ii: 585–88.

6 Sommer A, Tarwotjo I, Djunaedi E, et al. Impact of vitamin A supplementation on childhood mortality: a randomised controlled community trial. *Lancet* 1986; i: 1169–73.

7 Muhilal, Permeisih D, Idjradinata YR, et al. Vitamin A-fortified monosodium glutamate and health, growth, and survival of children: a controlled field trial. *Am J Clin Nutr* 1988; **48:** 1271–76.

8 Rahmathullah L, Underwood BA, Thulasiraj RD, et al. Reduced mortality among children in Southern India receiving a small weekly dose of vitamin A. *N Engl J Med* 1990; **323:** 929–35.

9 West KP Jr, Pokhrel RP, Katz J, et al. Efficacy of vitamin A in reducing preschool child mortality in Nepal. *Lancet* 1991; **338:** 67–71.

10 Daulaire NMP, Starbuck ES, Houston RM, et al. Childhood mortality after a high dose of vitamin A in a high risk population. *BMJ* 1992; **304:** 207–10.

11 Vijayaraghavan K, Radhaiah G, Prakasam BS, et al. Effect of massive-dose vitamin A on morbidity and mortality in Indian children. *Lancet* 1990; **336:** 1342–45.

12 Herrera HG, Nestel P, El Amin A, et al. Vitamin A supplementation and child survival. *Lancet* 1992; **340:** 267–71.

13 Rahmathullah L, Underwood BA, Thulasiraj RD, Milton RC. Diarrhea, respiratory infections, and growth are not affected by a weekly low-dose vitamin A supplement: a masked, controlled field trial in children in Southern India. *Am J Clin Nutr* 1991; **54:** 568–77.

14 Abdeljaber MH, Monto AS, Tilden RL, et al. The impact of vitamin A supplementation on morbidity: a randomized community intervention trial. *Am J Publ Health* 1991; **81:** 1654–56.

15 Barclay AJG, Foster A, Sommer A. Vitamin A supplements and mortality related to measles: a randomised clinical trial. *BMJ* 1987; **294:** 294–96.

16 Hussey GD, Klein M. A randomized, controlled trial of vitamin A in children with severe measles. *N Engl J Med* 1990; **323:** 160–64.

17 Coutsoudis A, Broughton M, Coovadia HM. Vitamin A supplementation reduces measles morbidity in young African children: a randomized, placebo-controlled, double-blind trial. *Am J Clin Nutr* 1991; **54:** 890–95.

18 Irrigation Company of Upper Regions (ICOUR). Monthly rainfall statistics, 1981–90. Tono, Ghana, 1991.

19 Armitage P, Berry G. Statistical methods in medical research, 2nd ed. Oxford: Blackwell, 1987: 92.

20 Sommer A. Field guide to the detection and control of xerophthalmia, 2nd ed. Geneva: WHO, 1982.

21 Wolbach SB, Howe PR. Tissue changes following deprivation of fat-soluble vitamin A. *J Exp Med* 1925; **42:** 753–77.

22 Blackfan KD, Wolbach SB. Vitamin A deficiency in infants: a clinical and pathological study. *J Pediatr* 1933; **3:** 679–706.

23 Olson JA. The biological role of vitamin A in maintaining epithelial tissues. *Israel J Med Sci* 1972; **8:** 1170–78.

24 Chandra RK. Increased bacterial binding to respiratory epithelial cells in vitamin A deficiency. *BMJ* 1988; **297:** 834–35.

25 Mohanram M, Reddy V, Mishra S. Lysozyme activity in plasma and leucocytes in malnourished children. *Br J Nutr* 1974; **32:** 313–16.

26 Bhaskaram C, Reddy V. Cell mediated immunity in iron and vitamin deficient children. *BMJ* 1975; **3:** 522.

27 Friedman A, Sklan D. Antigen-specific immune response impairment in the chick as influenced by dietary vitamin A. *J Nutr* 1989; **119:** 790–95.

28 West KP, Sommer A. Delivery of oral doses of vitamin A to prevent vitamin A deficiency and nutritional blindness: a state-of-the-art review. Rome, Italy; United Nations Administrative Committee on Coordination, Subcommittee on Nutrition, Nutrition Policy Discussion Paper No. 2, 1987.