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Vitamin A supplementation in infectious diseases: a meta-analysis

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Abstract

Objective—To study the effect of vitamin A supplementation on morbidity and mortality from infectious disease.

Design—A meta-analysis aimed at identifying and combining mortality and morbidity data from all randomised controlled trials of vitamin A.

Results—Of 20 controlled trials identified, 12 trials were randomised trials and provided "intention to treat" data: six community trials in developing countries, three in children admitted to hospital with measles, and three in very low birth weight infants. Combined results for community studies suggest a reduction of 30% (95% confidence interval 21% to 38%; two tailed $p < 0.0000001$) in all cause mortality. Analysis of cause specific mortality showed a reduction in deaths from diarrhoeal disease (in community studies) by 39% (24% to 50%; two tailed $p < 0.00001$); from respiratory disease (in measles studies) by 70% (15% to 90%; two tailed $p = 0.02$); and from other causes of death (in community studies) by 34% (15% to 48%; two tailed $p = 0.001$). Reductions in morbidity were consistent with the findings for mortality, but fewer data were available.

Conclusions—Adequate supply of vitamin A, either through supplementation or adequate diet, has a major role in preventing morbidity and mortality in children in developing countries. In developed countries vitamin A may also have a role in those with life threatening infections such as measles and those who may have a relative deficiency, such as premature infants.

Introduction

In 1928 Green and Mellanby noted that though vitamin A was then known as the growth promoting vitamin, evidence from animal studies showed it was also an anti-infective vitamin.¹ Four years later, Ellison reported a controlled trial of 600 English children hospitalised with measles which showed that cod liver oil reduced mortality by 58%.² But the role of vitamin A in preventing xerophthalmic blindness, combined with the discovery of antibiotics, overshadowed its possible anti-infective role.

In 1986 Sommer *et al* reported a seminal randomised trial showing a 34% reduction in the all cause mortality of preschool Indonesian children without florid signs of deficiency as a result of two 200 000 IU doses of vitamin A given six months apart.³ Several months later Barclay *et al* reported a 50% reduction in mortality in children hospitalised with measles, although this result was not statistically significant.⁴ A recent large randomised study in India found no such effect but rather an apparent slight excess of deaths in the supplemented group.⁵ In the subsequent exchange of letters it was asserted that there is no evidence that high doses of vitamin A reduce the rate of infection and, as a mechanism was lacking, the effect on mortality was equally suspect.^{7,8}

Given the magnitude of the apparent benefit and the simplicity and inexpensiveness of the intervention, clarification of the role of vitamin A is of considerable importance. We therefore performed a meta-analysis of the available randomised trials of vitamin A supplementation, looking at total mortality, cause specific mortality, and morbidity from infectious diseases.

Methods

IDENTIFICATION OF TRIALS

We aimed to examine and combine all randomised controlled trials of vitamin A supplementation for the prevention of death or morbidity from infectious disease, in particular respiratory and gastrointestinal disease. Two methods were used to locate primary research data. Medline was searched independently by one of the authors, a research assistant, and a librarian for the years 1969 to 1992, using combinations of the following key words: vitamin A, respiratory disease, diarrhoea, random allocation, and clinical trial. In addition, the references of the available primary studies, review articles, and editorials were checked to identify references not found in the Medline searches.

A report was dropped from further analysis if the study did not include concurrent controls or contained no original data or if the report did not address mortality, respiratory disease, or diarrhoea. Several trials that looked at cancer prevention were not considered within the scope of this analysis. On the basis of these initial broad criteria, clearly irrelevant articles were discarded after consideration by a single reviewer.

The methods sections of the potentially relevant reports were then extracted with reference to results and identifying material (authors, title, journal, institution, and country of origin) removed. These methods sections were assessed independently by two reviewers with respect to randomisation (individual, cluster, or none), use of a placebo, loss to follow up, measuring outcome blind to treatment assigned. Papers that did not include a control group, were not randomised, did not allow calculation of "intention to treat" results, or did not collect information on mortality or the incidence of respiratory or gastrointestinal infection were excluded.

STATISTICAL METHODS

We extracted from each trial data for an analysis by intention to treat—that is, an analysis that retains all individuals within the group to which they were randomised, regardless of compliance. Regrouping of data was necessary for one trial: table III of that paper was used to calculate the deaths in each group irrespective of the dose of vitamin A actually received.⁵

The Mantel-Haenszel estimate of the overall odds ratio and its variance were calculated from a set of studies by the Robins-Breslow-Greenland method.⁹ To test whether the variation between studies was explicable by chance, the Breslow and Day approxima-

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tion¹⁰ for Zelen's homogeneity statistic was used. All calculations were done with StatExact.¹¹

One concern with any meta-analysis is that statistically non-significant studies are less likely to be submitted for publication¹² and hence that the results of combining published studies is biased towards a positive effect. To examine the potential for such publication bias, we calculated Rosenthal's "file drawer" N, which is an estimate of the number of similar sized, but unpublished, studies with no effect (that is, an odds ratio of 1) needed to render the meta-analysis result no longer statistically significant.¹³

Results

Table 1 shows the 20 controlled trials identified and gives details of the population and methods of these trials. Most were community based trials of children in developing countries, with children who had overt vitamin A deficiency excluded. The included studies fell into three distinct groups: six community based trials, three trials of children hospitalised with measles, and three trials in very low birthweight infants.

Eight of the 20 controlled studies were excluded: four were not randomised, three did not provide intention to treat data, and one did not provide sufficient outcome data. Ellison's 1932 British study of measles showed a significant mortality reduction, but the patients were allocated by the ward to which they had been admitted.² The other non-randomised studies were three community studies. Of particular interest was the Indonesian community study that used fortified monosodium glutamate, rather than capsule supplementation, in five programme villages, with five other villages used as controls.²⁷ This showed a reduction in mortality in the programme villages: the odds ratio for death was 0.69 (95% confidence interval 0.57 to 0.84; $p=0.004$). The largest excluded study was conducted in Sudan but used an allocation method whereby the families given vitamin A and placebo were recruited by two separate researchers.³⁰ Thus, differential abilities to recruit may cause selection biases; indeed the baseline results in this study showed highly significant differences in important confounders—for example, household cleanliness was worse in the vitamin A group ($p<0.0001$), indicating a failure of randomisation by this procedure. A recent randomised trial from Ghana was described in a letter but details on loss to follow up, on use of an intention to treat analysis, and on several end points, including

mortality, were missing.²⁹ Similarly, a recent study in Bangladesh excluded an unknown number of poor compliers and did not describe mortality.³¹

A randomised trial of children in South Australia who were prone to recurrent respiratory infections showed a reduction in respiratory events for those taking vitamin A, but not a reduction in total days of illness.²⁵ A subsequent trial in children previously infected with respiratory syncytial virus showed no reduction in either incidence or days of symptoms.²⁶ However, in both trials almost a third of randomised individuals were excluded from the analysis either because of loss to follow up or insufficient compliance with medication, and an analysis by intention to treat could not be reconstructed from the data presented nor from data still with the principal author (personal communication). Inclusion of any of these studies would have made little difference to our conclusions about mortality reduction.

ALL CAUSE MORTALITY

Table II shows the death rates for trials that reported at least one death. One community study looked at the incidence of respiratory and diarrhoeal disease but reported no mortality.²¹ The overall mortality reduction in the five included community studies (fig 1) was highly significant, both statistically (two tailed $p<0.0000001$) and clinically: a common odds ratio of 0.70 (0.62 to 0.79; confidence interval not adjusted for cluster design of community studies) indicating a risk reduction of 30%—that is, a reduction of about a third in mortality from all causes. The test for homogeneity in the five community studies did not suggest any significant differences among them ($p=0.16$).

The three studies we included of children hospitalised with measles were of the highest quality—placebo controlled, individually randomised, and with complete follow up—and also showed a somewhat greater mortality benefit than the community studies: an odds ratio of 0.34 (0.15 to 0.77)—that is, a risk reduction of 66%. This may in part be explained by the lower compliance in the community studies: using intention to treat analysis results in a diluting of effect when compliance is low. Sommer and Zeger have estimated that if full compliance had been achieved in the Aceh study³ the reduction in mortality in months 4 to 12 would have been 72% rather than the 41% given by the intention to treat analysis.³² This estimate is close to that of the combined measles studies.

Two community or measles studies that we included

TABLE 1—Controlled trials of vitamin A in infectious diseases

Trial	Year	No of children	Country	Health state	Age (years)	Placebo	Randomisation	Loss to follow up (%) (vitamin A; control)
<i>Included in analysis</i>								
Sommer <i>et al</i> , ³ Abdeljaber <i>et al</i> ⁴	1986	29 236	Indonesia	Well	0-6	No	450 Clusters	11; 12
Barclay <i>et al</i> ⁵	1987	180	Tanzania	Measles	0-5	No	Individual	Nil
Shenai <i>et al</i> ⁶	1987	40	United States	VLBW infants	0	Yes	Individual	Nil
Papagaroufalos <i>et al</i> ⁷	1988	37	Greece	VLBW infants	0	Yes	Individual	Nil
Papagaroufalos <i>et al</i> ⁷	1991	47	Greece	VLBW infants	0	Yes	Individual	Nil
Hussey and Klein ¹⁸	1990	189	South Africa	Measles	< 13	Yes	Individual	Nil
Vijayaraghavan <i>et al</i> ⁸	1990	15 775	India	Well	1-5	Yes	84 Clusters	8; 13
Rahmattullah <i>et al</i> ²⁹	1990	15 419	India	Well	0-5	Yes	206 Clusters	< 12; < 12
Bloem <i>et al</i> ²¹	1990	166	Thailand	Well	1-5	No	Individual	14
West <i>et al</i> ²²	1991	24 805	Nepal	Well	0-5	Yes	29 Clusters	4; 4
Coutsoudis <i>et al</i> ²³	1991	60	South Africa	Measles	0-67-2	Yes	Individual	Nil
Daulaire <i>et al</i> ⁹	1992	7 197	Nepal	Well	< 5	No	16 Districts	≤ 1
<i>Excluded from analysis</i>								
Ellison ²	1932	600	United Kingdom	Measles	0-5	No	Allocated by ward	Nil
Pinnock <i>et al</i> ²⁴	1986	147	Australia	Prone to respiratory infections	1-4	Yes	Individual	30; 24*
Pinnock <i>et al</i> ²⁴	1988	206	Australia	Past bronchiolitis	2-7	Yes	Individual	24; 31*
Muhilal <i>et al</i> ²⁷	1988	11 220	Indonesia	Well	0-5	No	None: 10 clusters	< 30
Kothari ²⁸	1991	4 277	India	Well	0-5	No	2 Areas	2; 4
Arthur <i>et al</i> ²⁹	1992	1 455	Ghana	Well	0-50-5	Yes	Individual	Not stated
Herrera <i>et al</i> ³⁰	1992	29 615	Sudan	Well	0-75-6	Yes	Alternate allocation	< 1
Henning <i>et al</i> ³¹	1992	83	Bangladesh	Diarrhoea	1-5	Yes	Individual	Unknown

VLBW=very low birthweight.

*These were excluded because of poor compliance.

TABLE II—Number of deaths from all causes and mortality in studies that had at least one death

Study	Dose regimen	Group given vitamin A		Control group	
		Deaths/total	Rate (%)	Deaths/total	Rate (%)
Included in analysis					
Community:					
Sommer <i>et al</i> ⁵	200 000 IU six-monthly	101/12 991	0.8	130/12 209	1.1
Vijayaraghavan <i>et al</i> ⁶	200 000 six-monthly	39/7076	0.6	41/7006	0.6
Rahmathullah <i>et al</i> ^{19, 20}	8 333 IU weekly	37/7764	0.5	80/7755	1.0
West <i>et al</i> ²²	200 000 IU four-monthly	152/12 541	1.2	210/12 264	1.7
Daulaire <i>et al</i> ²⁴	200 000 IU once	138/3786	3.6	167/3411	4.9
Measles:					
Barclay <i>et al</i> ⁴	200 000 IU twice	6/88	6.8	12/92	13.0
Hussey and Klein ¹⁸	200 000 IU twice	2/92	2.2	10/97	10.3
Coutsoudis <i>et al</i> ²³	360 000 IU thrice	0/29		1/31	
Very low birthweight infants:					
Shenai <i>et al</i> ¹⁵	2 000 IU/2 days intramuscularly (×14)	1/20		0/20	
Papagaroufalis <i>et al</i> ¹⁶	4 000 IU/2 days intramuscularly	6/19	31.6	5/18	27.8
Papagaroufalis <i>et al</i> ¹⁷	3 750 IU/2 days intramuscularly (×8)	4/23	17.4	8/24	33.3
Excluded from analysis					
Community:					
Kothari ²⁸	200 000 IU once	8/2217	0.4	39/2060	1.9
Muhilal <i>et al</i> ²⁷	Fortified monosodium glutamate	186/5775	3.2	250/5445	4.6
Herrera <i>et al</i> ³⁰	200 000 IU six monthly	120/14 343	0.8	112/14 149	0.8
Measles:					
Ellison ²	Cod liver oil	11/300	3.7	26/300	8.7

had more than a single death and were not individually statistically significant: those by Barclay *et al*⁴ and Vijayaraghavan *et al*.⁵ The point estimate for the study by Barclay *et al* is close to the combined estimate; that by Vijayaraghavan showed least effect but also had the lowest mortality in the control group, and its confidence intervals include the overall community study reduction of 30%.

Figure 2 shows the excluded studies in which some deaths occurred. The overall result for the three community studies is almost identical to that of the included studies (odds ratio 0.74; 0.64 to 0.86) but showed significant heterogeneity ($p < 0.0001$). We cannot know whether this is due to difference in the real effect or differences in degree of bias.

One remaining concern is publication bias—that publication has favoured those trials with positive results. We therefore calculated the “fail safe N,” the number of negative papers that would be required to overturn this result, based on the five included community studies with any deaths. This was 53, which would mean that 53/(53+5)=91% of all trials of the effect of vitamin A on childhood mortality would need to be unpublished. This seems unlikely; hence the overall evidence for a reduction in mortality is strong.

CAUSE SPECIFIC MORTALITY

Of the included studies, three of the five community trials plus two of the three measles trials reported cause

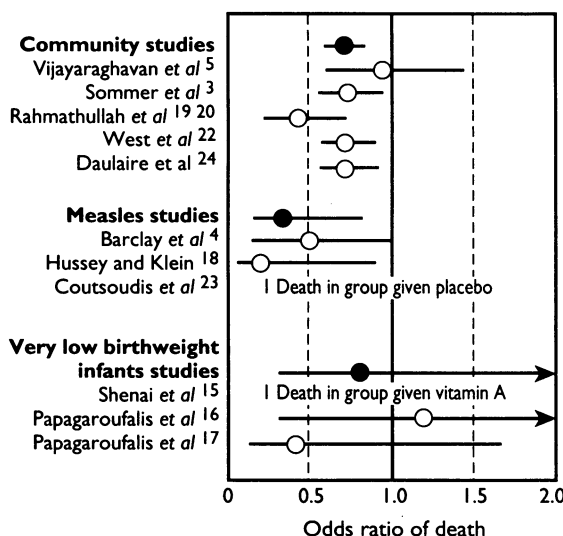


FIG 1—All cause mortality. Open circles are odds ratios for individual studies; solid circles are summary odds ratios for combined studies

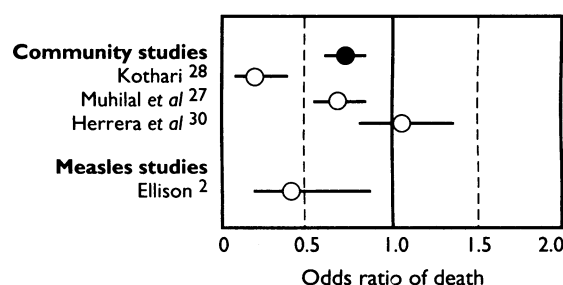


FIG 2—All cause mortality in studies excluded from analysis. Open circles are odds ratios for individual studies; solid circles are summary odds ratios for combined studies

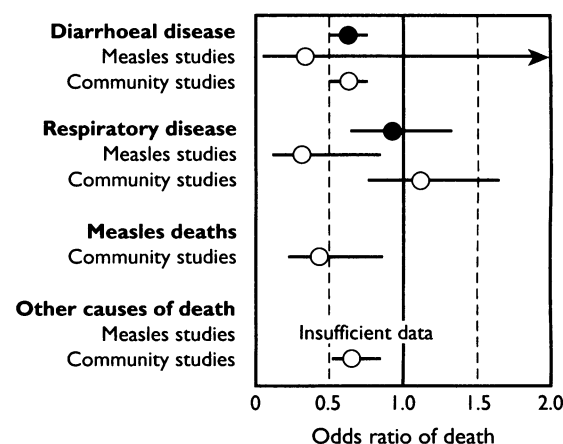


FIG 3—Cause specific mortality. Two of six community trials were omitted as no cause specific data were reported (Sommer, Vijayaraghavan). Measles trials are summarised in text

specific mortality. The third measles trial¹⁸ reported that of the 12 deaths (10 in controls, two in those given vitamin A), 10 were due to respiratory disease. We used the conservative assumption that both children given vitamin A and hence eight of the 10 controls died from respiratory disease.

Figure 3 shows the combined data on cause specific mortality. The community trials combined show a 39% reduction in diarrhoeal deaths (24% to 50%; two tailed $p < 0.00001$), a 55% reduction in measles deaths (13% to 77%; two tailed $p = 0.017$), and a slight increase in respiratory deaths, though this was not significantly different from an odds ratio of 1. Most interestingly, the community trials showed a 34% reduction in other causes of death (15% to 49%; two tailed $p = 0.0001$), excluding diarrhoea, respiratory causes, and measles. The three measles studies combined show a 70%

reduction in deaths from respiratory causes (15% to 90%; two tailed $p=0.02$) and a reduction in deaths from diarrhoea consistent with the community trials but with very wide confidence intervals.

EFFECTS ON MORBIDITY

Morbidity has been less extensively studied. Only six of the studies reported results for respiratory or diarrhoeal morbidity: three of the community trials, two of the measles trials, and one of the trials in very low birthweight infants.

Data on morbidity were reported in a variety of ways, and the results in table III are a mixture of prevalence,¹⁴ incidence,²¹ and episode duration (measles studies). Hence overall summary measures have not been presented. However, the results show either a decrease in morbidity or no change, suggesting effects at least in some circumstances. In particular, morbidity for those hospitalised with measles is clearly reduced.

The trial by Shenai *et al* showed a reduction in lower respiratory tract infections from 55% in the control group to 21% in the vitamin A group ($p<0.029$).¹⁵ Two of the three studies of very low birthweight babies also showed significant reductions in the incidence of bronchopulmonary dysplasia and duration of ventilator requirements.^{15,16} These were both double blinded trials with the control group receiving placebo injections; hence reductions in ventilator requirements cannot be explained by the investigator's knowledge of treatment.

Discussion

These results show clear evidence that vitamin A reduces all cause mortality in children in developing countries by around one third. A similar but apparently stronger effect is seen in children hospitalised with measles, with a reduction of 66%, although this was not significantly different from the 30% seen in developing country community settings. Of note is that the study by Vijayaraghavan *et al*⁵ is consistent with this overall effect: the confidence interval of that study included this 30% reduction, and the test of homogeneity did not suggest a difference between studies. The sum of evidence is now too strong to justify further placebo controlled trials in communities with vitamin A deficiency. Rather, optimal methods of delivery should be explored—for example, dietary alteration, supplementation through other products such as monosodium glutamate, or supplementation before peak incidence periods or in high risk groups such as refugee camps.

Daulaire calculated that one death was prevented for every 55 children given supplements.²⁴ The other communities studied all had lower death rates, and hence this "number needed to treat" would be higher. Patel has recently calculated that vitamin A supplementation is among the most cost effective interventions in developing countries, with a cost of around \$95

per life saved, compared with \$230 for oral rehydration and \$850 for measles vaccination.³³

Although capsule distribution could be linked to other programmes such as immunisation, it must be given two to three times a year to achieve continuous coverage, and the risk of toxicity also needs consideration. Without other support programmes to improve dietary and general health and hygienic conditions, capsule distribution has had poorer results than anticipated in controlling xerophthalmia.³⁴ Reductions in mortality similar to that found by our meta-analysis have also been seen in the controlled (non-randomised) study by Muhilal *et al*,²⁷ achieved by fortifying monosodium glutamate supplied to villages; this maintains retinol levels better than infrequent high doses. Such food fortification programmes would seem to be the most practical method in countries where no major improvement in dietary intake is anticipated. Clearly, in the long term, improving dietary habits and food supply is the most desirable approach.

The other major target group is those hospitalised with infectious illnesses. The results of this meta-analysis confirm the 1987 World Health Organisation recommendation to give vitamin A to children with measles in countries where vitamin A deficiency is a recognised problem³⁵—a statement released when only the results of Barclay *et al*'s study, which were not statistically significant,⁴ and of that by Ellison, which was non-randomised,² were available, but the sum of current evidence is now too strong to justify further trials in hospitalised measles patients in developing countries. Furthermore, since Hussey *et al*¹⁸ showed that hospitalisation was decreased by an average of 4.7 days,¹⁸ supplementing children hospitalised with measles is likely to be not only effective but also cost saving. Whether this is true in developed countries is yet to be seen: although Ellison's 1932 study in the United Kingdom is consistent with the results in figure 1, it preceded immunisation and antibiotics and hence is not comparable in 1992.

An incompletely resolved puzzle is the mechanism by which vitamin A reduces mortality. The two major causes of death in children hospitalised with measles and in the community settings were respiratory and diarrhoeal disease. The overall mortality from diarrhoea was significantly reduced, whereas a reduction in deaths from respiratory disease was seen only in the measles studies. This reduction in deaths from pneumonia was also noted in Ellison's 1932 study.² Perhaps the most interesting finding, however, was that other causes of death were reduced by about 34%. This has two possible explanations. Firstly, the other causes of death may have included a high proportion of respiratory or diarrhoeal deaths that had been misclassified—for example, the cause of death in the trial by West *et al* was ascertained from a verbal necropsy report.²² Secondly, vitamin A may indeed affect other causes of death: the causes reported most frequently were malnutrition, other infectious illness, and convulsions. Although this result is not significant, it is

TABLE III—Morbidity results in studies included in analysis that reported data on either respiratory or diarrhoeal morbidity

Study	Respiratory infection		Diarrhoea	
	Measure	Odds ratio (95% confidence interval)	Measure	Odds ratio (95% confidence interval)
<i>Community:</i>				
Rahmathullah <i>et al</i> ²⁰	Incidence of lower respiratory tract infection	1.01 (0.73 to 1.40)	Incidence	0.99 (not given)
Bloem <i>et al</i> ^{1*}	Incidence of respiratory tract infection	0.54 (0.30 to 0.97)	Incidence	0.89 (0.50 to 1.6)
Abdeljaber <i>et al</i> ⁴	Prevalence of cough	0.89 (0.54 to 1.46)	Prevalence	0.88 (0.32 to 2.16)
<i>Measles:</i>				
Hussey and Klein ¹⁸	Pneumonia ≥ 10 days	0.44 (0.24 to 0.80)	≥ 10 Days	0.40 (0.19 to 0.86)
Coutsoudis <i>et al</i> ¹	Duration of pneumonia	-1.9 days (-0.3 to -3.0)†	Duration	-1.3 days (-2.5 to 0.6)†
<i>Very low birthweight infants:</i>				
Shenai <i>et al</i> ⁵	Airway infection	0.27 (0.07 to 1.1)		

*Stratified analysis based on table 4 in reference.

†Group given vitamin A minus control group.

within the confidence limits for the mortality from the combined measles studies (see fig 1).

All reported morbidity results showed some reduction in the groups given vitamin A supplements (see fig 3), though the only significant results were the duration of illness in the measles trials and the incidence of respiratory illness in the Thailand trial.²¹ Coutosoudis *et al* also found fewer and less severe episodes of illness in a six month post discharge follow up of the supplemented group who had had measles.²³ The Ghanaian trial reported no differences in incidence of 19 of 21 symptoms but found a 38% reduction in hospital admissions for the supplemented group.²⁹ The two Indian community studies found no significant effect on incidence^{25,20} or the duration and severity²⁰ of diarrhoea and pneumonia. The available trial results are consistent with a shift in the spectrum of illness to being less severe, of shorter duration, and with a greater proportion of subclinical disease. It would have been useful if the various studies had reported all morbidity results (whether "statistically significant" or not) and in a compatible format.

What applications might these results have in developed countries where vitamin A is plentiful? It would seem that there are few general applications, but several specific conditions may be helped by higher doses of vitamin A. Firstly, though, it should be remembered that retinol is toxic in large doses, and the public should not be given the impression that it is a safe supplement for children who may have recurrent respiratory or diarrhoeal illness. The only evidence to date regarding respiratory illness is that of Pinnock *et al* (see table I), which was equivocal.^{25,26}

In the case of very low birthweight infants, two trials showed reductions in incidence of bronchopulmonary dysplasia and respiratory infection and of duration of ventilation and stay in intensive care.^{15,16} Other groups with possible relative deficiency would be those with malabsorption and acute or chronic infection. Hence, in developed countries research should focus on high risk groups, such as Australian aboriginal children (who have considerable respiratory tract illness) and other disadvantaged groups, those with severe infectious illnesses such as measles, and those with chronic illnesses such as cystic fibrosis and AIDs that are prone to infections. Finally, we note that all of the reviewed studies used retinol at doses near the recommended daily intake as the source of vitamin A. Therefore the results should not be confused with the many cancer prevention trials that are investigating the effects of high dose β carotene.

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