Potential interventions for the prevention of childhood pneumonia in developing countries: a meta-analysis of data from field trials to assess the impact of vitamin A supplementation on pneumonia morbidity and mortality*

The Vitamin A and Pneumonia Working Group[1]

Reported are the results of a meta-analysis (12 large-scale field trials in seven countries) of the impact of vitamin A supplementation on pneumonia morbidity and mortality, undertaken as part of a wider review process of a range of possible potential interventions for the prevention of childhood pneumonia. The summary estimate of the relative risk for the impact of vitamin A supplementation on pneumonia incidence was 0.95 (95% confidence interval (CI) = 0.89, 1.01), and for pneumonia mortality, 0.98 (95% CI = 0.75, 1.28). This is in marked contrast to the substantial impact of vitamin A supplementation on all-cause mortality (combined rate ratio (RR) = 0.77, 95% CI = 0.71, 0.84), and on diarrhoea-specific and measles-specific mortality. There was no evidence for a differential impact on pneumonia mortality by age. Since the majority of pneumonia deaths occur in the first year of life, we complemented the paucity of data on pneumonia-specific mortality among this age group with a detailed examination of all-cause mortality among infants. The mortality reduction in the 6–11-month age group was consistent with that observed for older age groups (RR = 0.69; 95% CI = 0.54, 0.90), but there was no reduction for 0–5-month-olds (RR = 0.97; 95% CI = 0.73, 1.29).

* This publication is part of a series of reviews of potential interventions for the prevention of childhood pneumonia among under-5-year-olds in developing countries, being carried out by the WHO Programme for the Control of Acute Respiratory Infections (WHO–ARI) and the Maternal and Child Epidemiology Unit, London School of Hygiene and Tropical Medicine (MCEU–LSHTM), with support from the United Kingdom Overseas Development Administration, WHO, and UNICEF. The aim is to identify selected nutritional, environmental, behavioural and vaccine interventions that can be expected to have a significant impact on pneumonia morbidity and mortality in children.

Vitamin A deficiency is one of 22 risk factors that have been reviewed. The meta-analysis is a more detailed follow-up to an initial review of the literature and biological plausibility which was carried out by A. Tomkins and K. Southwick, Institute of Child Health, London, as part of the general activities of the review series. It was undertaken by a working group that included the principal investigators of all the large-scale field studies which had been completed up to January 1993. Analyses were carried out within the individual studies using data analysis protocols prepared by LSHTM and agreed at a meeting convened by WHO–ARI in Geneva in November 1992. The results were summarized and conclusions agreed at a second meeting in Geneva in February 1993 (See: *Vitamin A supplementation and childhood pneumonia: report of a meeting, Geneva, 1–3 February 1993.* Unpublished document WHO/CDR/93.2, 1993).

Reprint No. **5640**

[1] The composition of the working group was as follows: ACEH (Indonesia) study: A. Sommer; MADURAI (India) study: L. Rahmathullah, B. Underwood, and R. Milton; HYDERABAD (India) study: V. Reddy; SARLAHI (Nepal) study: K. West; JUMLA (Nepal) study: N. Daulaire, T. Stukel; SUDAN study: G. Herrera; HAITI study: S. Stansfield; Ghana VAST (survival study): D. Ross; Ghana VAST (health study): B.R. Kirkwood, P. Arthur, and S. Morris; MORVITA (Indonesia) study: C. Kjolhede, M. Dibley; BAHIA (Brazil) study: M. Barreto; DELHI (India) study: M.K. Bhan; and WHO–ARI: S. Gove.

The meta-analysis was coordinated and the manuscript prepared by P. Arthur, B.R. Kirkwood, and S. Morris, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, England; and by S. Gove, Programme for the Control of Acute Respiratory Infections, World Health Organization, 1211 Geneva 27, Switzerland. Requests for reprints should be sent to Dr Gove at the latter address. Other correspondence should be sent to Professor Kirkwood at the London School of Hygiene and Tropical Medicine.

Background

Several histopathological changes to epithelial tissue following vitamin A depletion have been described which suggest that vitamin A deficiency (VAD) might predispose to respiratory infections. Widespread keratinization of the epithelium in the nose, sinuses, larynx, trachea and bronchi in rats (*1*), autopsy findings of keratinizing metaplasia of the respiratory tract in children (*2*), and electron microscopy studies showing early, rapid squamous metaplasia with loss of ciliary and goblet cells in rats (*3*) have all established that vitamin A is essential to the normal growth and differentiation of respiratory tract epithelium. Reduced lysozyme activity that responds to vitamin A therapy has also been observed in children (*4*). These changes result in a reduction of the trapping and clearing of airborne pathogens and irritants, and an increase of bacterial binding to respiratory epithelial cells (*5*). The physical and biological integrity of epithelial tissue, which is the first barrier to infection, is thus compromised in vitamin A deficiency and this would be expected to result in an increase in the incidence of respiratory infections.

Abnormalities in systemic immunity also occur. These include changes in the mass and maturation of lymphoid tissue, abnormal production of immune response regulators, reduced natural killer cell activity, and abnormal phagocyte and cytotoxic function and antibody production (*6–9*). Although the changes are less clear and varied for the different components of the immune system, the net effect appears to be a depression of the specific response to infection once the epithelial barriers have been breached.

Consistent with these results are findings from longitudinal field observational studies that children with VAD have an increased risk of acute respiratory infections (*10–12*). Clinical studies have also shown that the severity of illness and case fatality are reduced when vitamin A is administered to children with measles (*13–16*). It has therefore been hypothesized that improving the vitamin A status of children who are vitamin A deficient should lead to a reduction in respiratory morbidity and mortality. If this proves to be the case, promoting vitamin A programmes would be a potential strategy for the control of childhood pneumonia, which alone accounted for nearly 3.6 million out of the 12 million childhood deaths that occurred in developing countries in 1990 (*17*).

In an initial review in February 1992, we examined the relationship between VAD and childhood pneumonia and the impact of vitamin A supplementation on pneumonia. At that time there were few published studies on this topic. Those studies that had been carried out had primarily evaluated the impact of vitamin A on overall childhood mortality, and contained very little information on pneumonia-specific morbidity and mortality. Data from six field trials in Indonesia, India, and Nepal were reviewed (*18–23*), which showed large reductions in overall childhood mortality following supplementation with vitamin A.

A large beneficial impact on all-cause mortality cannot be expected without an impact on the leading causes of childhood deaths, i.e., pneumonia and diarrhoea, which together account for more than 60% of all childhood deaths in developing countries. However, although deaths due to diarrhoea and measles were reduced in these studies, there was no impact on deaths due to pneumonia. The data from the studies were not disaggregated by age, and an impact on pneumonia could have been missed because infants were underrepresented. Nearly 75% of nonprimary measles and pertussis pneumonia deaths among preschool-age children occur in infants — up to 58% before 6 months of age. Except for the two studies in Nepal, all the others were of children above 6 months of age (6–72 months), and individual studies had covered insufficient numbers of children in the most vulnerable age group to detect an impact on pneumonia. Data from a set of more recent field studies that were completed in 1991, including four studies that had conducted a detailed evaluation of the impact on morbidity and one that included young infants, permitted a more detailed examination of the relationship between VAD and childhood pneumonia.

We have reviewed the impact of vitamin A supplementation on pneumonia morbidity and mortality using a meta-analysis of the pooled data from large-scale field trials completed by January 1993. The objectives were to obtain estimates of the effect of supplementation on pneumonia mortality and to examine whether vitamin A supplementation has any impact (positive or negative) on the incidence and prevalence of childhood pneumonia. Of particular interest, was the impact if any, among infants, the group at highest risk from pneumonia mortality. The findings of the review are described in this article.

Methods

The principal investigators of 12 completed large-scale field trials (published and unpublished) that collected data on acute respiratory infection (ARI) morbidity and/or mortality contributed data to the review. Seven studies were conducted in Asia (India (3 studies), Indonesia (2), Nepal (2)); three in Africa (Ghana (2), Sudan); and one each in Brazil and Haiti. The study sites differed in terms of their affluence

and indicators of health, nutritional status and vitamin A profile — from areas of relatively high affluence and zero prevalence of xerophthalmia (Brazil) to extremely deprived areas with very high rates of xerophthalmia (JUMLA, in Nepal; MADURAI, in India).

The main characteristics of the sites and the study design features are summarized in Table 1. All the trials used oral doses of vitamin A, ranging from weekly low doses (MADURAI) to 6-monthly high doses (ACEH, HYDERABAD and SUDAN). In two of the trials (JUMLA and DELHI) only a single high-dose supplement was administered, with a relatively short period of follow-up of children (5 months and 3 months, resp.). The four trials that primarily evaluated morbidity end-points (BAHIA, DELHI, VAST–CHS and MORVITA) were all randomized at the level of the individual child, and those that evaluated the impact on mortality (ACEH, HYDERABAD, MADURAI, JUMLA, SARLAHI, SUDAN and VAST–CSS) were randomized on larger units, such as households, villages, clusters of villages, or other administrative or geographical divisions. The HAITI study was similar in design to the mortality studies, but only provided data on morbidity. All of these studies were field trials with supplementation of the general child population, except for the DELHI trial, which was restricted to children with acute diarrhoea who were recruited from a clinic.

All of the trials included children aged ≥6 months, except for HYDERABAD and DELHI (≥12 months of age), but only two (SARLAHI and JUMLA) systematically included infants under 6 months of age. The SARLAHI study provided 16 months' data on young infants out of a total of 24 months' follow-up (data cleaning for the last few months of the trial was still in progress when the meta-analysis was performed).

A detailed protocol for standardized data analysis (available on request) was prepared in consultation with the principal investigators and standard definitions were agreed. In some cases these differed slightly from those used in the primary analyses of the individual studies. Pneumonia was defined as reported cough plus fast breathing, using a respiratory rate cut-off of >50 breaths per minute for infants and >40 breaths per minute for 1–4-year-olds. In the JUMLA study, however, a single respiratory rate cut-off of >50 breaths per minute was used for all children, and chest indrawing was also a sufficient condition for the diagnosis of pneumonia.

An episode was defined as beginning on the first day of coughing and either measured fast breathing or reported rapid breathing, and ending on the last day of the same combination of symptoms. A minimum of 14 days free from this symptom combination was required to define a new episode. If symptoms recurred in less than 14 days, those days of symptoms as well as the intervening symptom-free days, were considered to be part of the immediately preceding episode. Each episode was attributed to the age group the child was in when the episode started, and each child-week of follow-up was attributed to the age group to which the child belonged. Child-weeks of follow-up included all weeks when the child was seen by the field worker, as well as the weeks when the child was temporarily absent from home, but did not include periods when the child had moved away from the study area. Weeks of illness were not subtracted from the total weeks of follow-up. Asymptomatic days within episodes of pneumonia were not counted as positive days for the purpose of prevalence estimates.

Data on pneumonia-specific mortality were available from five out of the seven mortality studies and were based on cause of death obtained by verbal postmortem. Each death was attributed to the age group the child was in at the time of his/her death, and follow-up time was distributed between the various age groups the child passed through in the course of the study.

Combined estimates of the effect of vitamin A supplementation on pneumonia incidence and pneumonia mortality were obtained by Poisson regression using the number of deaths and child-years of follow-up in the two treatment groups as reported from each study. Where randomization was not at the individual level, the regression was weighted to allow for within-cluster homogeneity, using design effects (see Table 4) taken from the study by Beaton et al.[a] The results were not particularly sensitive to the precise choice of weightings. For the JUMLA study, in which 16 *panchayats* (geographical and administrative subdivisions) were sampled using a nonrandom procedure for allocation to the two treatment groups, adjustment factors were incorporated to accommodate substantial pre-trial differences between the vitamin A and placebo clusters. These factors were calculated using a longitudinal analysis incorporating pre-supplementation, post-supplementation and during supplementation periods by treatment group interaction term (T. Stukel, personal communication, 1993). It was not possible to adjust for within-individual clustering of pneumonia episodes in the morbidity analysis, and the quoted *P*-values for incidence rate ratios may therefore be underestimates.

[a] **Beaton GH et al.** *Effectiveness of vitamin A supplementation in the control of young child morbidity and mortality in developing countries.* Report submitted to Canadian International Development Agency, December 1992.

Table 1: **Characteristics of studies included in the meta-analysis**

Study/(*ref.*)	Sample size/ age group	Vitamin A status at baseline[a]	Dosing regimen	Surveillance	ARI data
BAHIA, Brazil	1 240/6–48 months (57 839 child-weeks)[b]	0% xerophthalmia 50% ret <0.70 µg/l	4-Monthly (× 3)	Home visits (×3 per week); referral if RR>40 min[c]	Pneumonia incidence + prevalence
DELHI, India	900/12–60 months	3.8% XN + X1B	Single dose	Home visits (x3 per week) for 90 days	Pneumonia incidence + prevalence
MORVITA, Indonesia	1400/6–48 months (78 202 child-weeks)[b]	0% xerophthalmia 59% ret <0.70 µg/l	4-Monthly (× 6)	48-Hour home visits; referral if RR>35 min[c]	Pneumonia incidence + prevalence
VAST-CHS, Ghana (*24*)	1 455/6–59 months (61 602 child-weeks)[b]	1.4% XN 0.2% X1B 15.3% ret <0.35 µg/l 72% ret <0.70 µg/l	4-Monthly (× 3)	Weekly home visits; clinic referral for probable ALRI	Pneumonia incidence + prevalence
HAITI (*25*)	11 124/6–83 months	0.1% X2+X3+XS	4-Monthly (× 3)	4-Monthly home visits	2-Weeks of ARI symptoms
ACEH, Indonesia (*23*)	25 200/12–71 months	0.7% XN 2.7% X1B	6-Monthly (× 2)	Cross-sectional surveys at start and 9–13 months later	Weekly prevalence of cough
HYDERABAD, India (*22*)	14 082/12–59 months	2% XN 4% X1B	6-Monthly (× 2)	3-Monthly home visits	4-Weeks of coughing
JUMLA, Nepal (*18*)	7 197/1–59 months (127 135 child-weeks)[b]	4.7% XN 8.2% X1B	Single dose	Case detection; death registration; verbal postmortem	Pneumonia incidence + mortality
MADURAI, India (*21*)	15 419/4–72 months (670 740 child-weeks)[b]	3.7% XN 7.2% X1B 19% ret <0.35 µg/l 36% ret <0.70 µg/l	Weekly (× 52)	Weekly home visits; verbal postmortem	Pneumonia mortality
SARLAHI, Nepal (*19*)	9 000/0–72 months (31 416 child-years)[b]	2.8% XN+X1B	4-Monthly	4-Monthly visits; verbal postmortem	Weekly prevalence of ARI symptoms; pneumonia mortality
SUDAN (*26*)	28 753/9–72 months	0.7 XN 2.7% X1B	6-Monthly (x3)	6-Monthly visits; verbal postmortem	Weekly prevalence of ARI symptoms; pneumonia mortality
VAST–CSS, Ghana (*24*)	21 906/6–95 months (33 287 child-years)[b]	1% XN 0.02% X1B 14% ret <0.35 µg/l 58% ret <0.70 µg/l	4-Monthly (× 6)	4-Monthly home visits; verbal postmortem	2-Weeks of ARI symptoms; ALRI mortality

[a] XN = night blindness; X1B = Bitot's spots; X2 = conjunctival xerosis; X3 = keratomalacia; XS = corneal scar; ret = serum retinol levels.
[b] Data in parentheses are person-time of follow-up.
[c] RR = measured respiratory rate (count per minute).

Results

Impact on pneumonia morbidity

Incidence of pneumonia. The number of episodes of pneumonia and the child-weeks of observation in the detailed morbidity studies and in the JUMLA study are shown in Table 2, as well as point estimates of the impact of supplementation. Only the rate ratio for JUMLA (0.77) showed a significant impact. The rate ratios in the other studies ranged from 0.92 (VAST–CHS) to 1.14 (MORVITA). The summary estimate of the impact on pneumonia incidence using data from all the studies was 0.95 (95% confidence interval (CI) = 0.89, 1.01); and 0.99 (95% CI = 0.92, 1.06) if the JUMLA study was excluded. The same analyses were repeated using a high breathing rate cut-off (50 breaths per minute) for all children, regardless of age, as was done in the JUMLA study. This resulted in a substantial decrease in the number of pneumonia episodes observed, especially in children over 2 years of age, but the conclusions regarding the impact of vitamin A supplementation remained unchanged.

Table 2: **Impact of vitamin A supplementation on pneumonia incidence**[a]

Study	Vitamin A			Placebo			Rate ratio
	No. of episodes	No. of child-weeks	Rate (per annum)	No. of episodes	No. of child-weeks	Rate (per annum)	
MORVITA	402	38 345	0.55	344	37 366	0.48	1.14 (0.99–1.32)[b]
BAHIA	544	29 000	0.98	557	28 839	1.00	0.97 (0.86–1.09)
DELHI	166	5 452	1.58	174	5 424	1.67	0.95 (0.77–1.17)
VAST-CHS	496	30 520	0.85	530	30 115	0.92	0.92 (0.82–1.04)
JUMLA[c]	797	67 520	0.61	1 047	59 615	0.91	0.77 (0.66–0.89)
Summary[d]	1 608	103 317		1 605	101 744		0.99[e] (0.92–1.06)
Summary[f]	2 357	172 146		2 623	162 541		0.95[e] (0.89–1.01)

[a] Tests for heterogeneity: (excluding JUMLA) χ^2 test = 5.13, 3 degrees of freedom, P = 0.161; (including JUMLA) χ^2 = 14.05, 4 degrees of freedom, P = 0.007.
[b] Figures in parentheses are the 95% confidence intervals.
[c] Estimates corrected for design effect and baseline differences between vitamin A and placebo groups.
[d] Summary of studies (JUMLA excluded).
[e] Mantel–Haenszel weighted rate ratio.
[f] Summary of studies (JUMLA included).

The age-specific estimates for the detailed morbidity studies are shown in Fig. 1. There was a slight trend with age, with a possible detrimental impact on pneumonia incidence among 6–11-month-olds and a possible beneficial impact on 48–59-month-olds. This trend was apparent to some degree in each of the four studies, but was not statistically significant. The confidence intervals in each of the age groups overlapped unity, even when the data were pooled across the studies. Most of the increased risk in the youngest age group was contributed by the data from the MORVITA study. The JUMLA data could not be disaggregated using the same age groupings, and were therefore analysed separately. There was a somewhat more pronounced trend with age; the rate ratio declined from 0.87 (95% CI = 0.72, 1.04) for the 3–11-month age group, to 0.73 (95% CI = 0.57, 0.93) for the 12–23-month age group, to 0.67 (95% CI = 0.52, 0.87) for the 24–59-month age group.

Fig. 2 shows the age-specific estimates of the impact of vitamin A supplementation on pneumonia incidence as defined by a combination of cough plus maternally reported rapid breathing (VAST–CHS and MORVITA studies) or cough, cold and fever plus rapid breathing or chest indrawing (MADURAI study). There was discordance between the positive impact reported by the VAST–CHS study and the detrimental impact reported by the other two studies. There was strong evidence of heterogeneity of effect between the different studies, and thus no attempt was made to summarize the results in a single estimate of the impact of vitamin A supplementation.

Prevalence of pneumonia. Two sources of data on the prevalence of pneumonia were available: daily prevalence data from the studies with intensive morbidity surveillance; and period prevalence data from the remaining studies. In the morbidity studies, in order to adjust for within-child clustering of illness episodes, prevalences were calculated for each child and for each dosing round separately, and the mean

Fig. 1. **Impact of vitamin A supplementation on pneumonia incidence, based on cough plus measured raised breathing rate.**

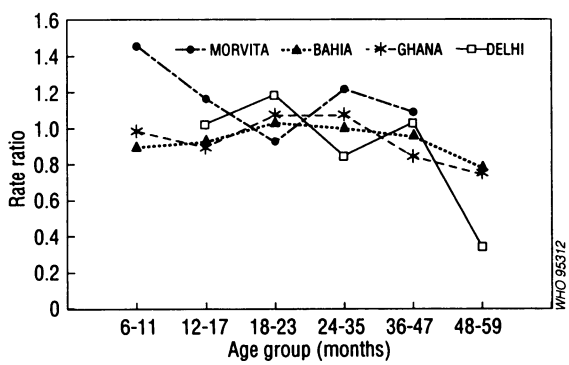
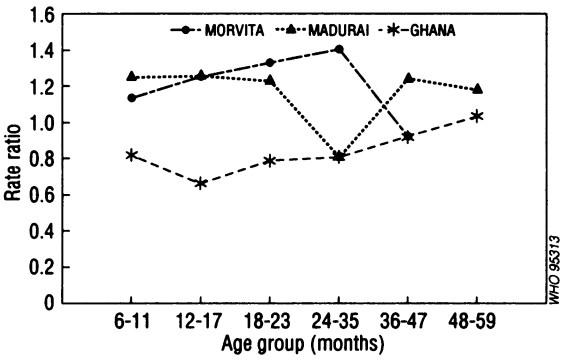


Fig. 2. **Impact of vitamin A supplementation on pneumonia incidence, based on cough plus maternal reporting of rapid breathing.**



prevalences were compared for the vitamin A and placebo groups. This analysis produced a pattern of age-specific impacts for prevalence (as defined by cough plus raised respiratory rate) identical to that shown for pneumonia incidence in Fig. 1. The data for the MORVITA and DELHI studies, however, displayed stronger negative impacts on the prevalence of pneumonia among the youngest age groups than seen for incidence, with a rate ratio as high as 1.73 in the youngest age group for the MORVITA study ($P = 0.08$). Nevertheless, overall, there was no suggestion of an important impact on pneumonia prevalence over the age range 6–59 months.

Two of the mortality studies also contributed data on the combination of cough plus (reported) rapid breathing. One-week-period prevalence data from the SARLAHI study collected 4 months after the last dose of vitamin A showed no impact in any age group. Two-week-period prevalence data from the HAITI study collected 2–6 weeks after the last scheduled dose, however, showed 20–25% increases in the risk of cough plus rapid breathing for most age groups, reaching statistical significance when all the age groups were combined.

The findings on the impact of supplementation on the prevalence of cough, and the combination of cough plus (reported) fever were also examined. The overall vitamin A:placebo ratio for the occurrence of cough was 0.99, and none of these studies suggested any impact—beneficial or deleterious — of vitamin A supplementation on the combination of cough plus fever.

Impact on pneumonia-specific mortality

There were clear differences in the verbal postmortem instruments applied, but the data were accepted, as provided by the various studies. A total of 296 pneumonia deaths were reported from five mortality trials. The rate ratios for pneumonia-specific mortality for the various studies and the summary estimate of the impact of supplementation for all the studies are shown in Table 3. The estimates are also contrasted with the effect estimates obtained for the impact on all-cause mortality.[b] The impact of vitamin A supplementation on pneumonia-specific mortality varied from a 57% decrease for the SUDAN study to a 10% increase for the SARLAHI and VAST–CSS studies, although confidence intervals included unity in all cases. However, the variation observed is not more than might reasonably be expected by chance if the true impact of vitamin A supplementation were uniform across study sites, and the pooled estimate of the effect on pneumonia mortality revealed no difference between the vitamin A and placebo groups (rate ratio (RR) = 0.98; 95% CI = 0.75, 1.28).

In four of the five studies considered, vitamin A supplementation had a markedly less protective effect on pneumonia mortality than on all-cause mortality. Indeed, in two of these studies (VAST–CSS and SARLAHI), a possibly detrimental effect on pneumonia mortality coexisted with a positive impact on all-cause mortality. There was an anomaly in the results from the SUDAN study, where an apparently large positive impact on pneumonia deaths was observed (RR = 0.43) despite an absence of impact on all-cause mortality (RR = 1.04).

The summary rate ratio from all five studies was very close to unity (0.98; 95% CI = 0.75–1.28). Age-specific estimates showed no evidence of a differential impact by age. The summary rate ratio was 0.96 (95% CI = 0.64, 1.45) among infants aged 1–11 months; 0.91 (95% CI = 0.55, 1.51) among children aged 12–23 months; and 1.07 (95% CI = 0.65, 1.78) among those aged 24–59 months. However, since most pneumonia deaths occur in infancy, this age group was examined in greater detail. Table 4 shows the number of pneumonia deaths and child-years of follow-up for the 0–5-month and 6–11-month age groups. Rate ratios of 0.88 and 1.08, respectively, were observed, although confidence intervals were very wide since there were only just over 50 deaths in each age group.

Since respiratory illness is such an important cause of death in infants, the paucity of data on pneumonia-specific mortality in this age-group was complemented by re-examining the all-cause mortality data in infants (Table 5). The mortality reduction for the 6–11-month age group was consistent with that observed for the older age groups (RR = 0.69; 95%

[b] See footnote *a*, p. 611.

Table 3: **Comparison of the impact of vitamin A supplementation on under-5-year-old pneumonia-specific mortality and on overall mortality**[a]

Study	Vitamin A			Placebo			Pneumonia-specific mortality		All-cause mortality
	No. of deaths	No. of child-years	Mortality rate (per 1000)	No. of deaths	No. of child-years	Mortality rate (per 1000)	Rate ratio	Design effect[b]	Rate ratio[c]
JUMLA	18	1 441	12.5	18	1 274	14.1	0.88	1.416 (0.38–2.05)[d]	0.74; *0.55–1.01*[e]
MADURAI	2	5 320	0.4	3	5 240	0.6	0.66	1.329 (0.08–5.19)	0.50; *0.34–0.75*
SARLAHI	77	17 867	4.3	68	17 339	3.9	1.10	1.187 (0.77–1.57)	0.71; *0.56–0.89*
SUDAN	6	15 223	0.4	14	15 162	0.9	0.43	1.000 (0.16–1.19)	1.04; *0.81–1.34*
VAST-CSS	47	11 988	3.9	43	12 116	3.5	1.10	2.003 (0.61–1.97)	0.80; *0.70–0.93*
Summary	150	51 839		146	51 131		0.98[f]	(0.75–1.28)	0.77; *0.71–0.84*

[a] Test for heterogeneity of effect between studies: χ^2 test = 3.938, 4 degrees of freedom, $P > 0.2$.
[b] Empirical design effect; see footnote *a*, p. 611.
[c] See footnote *a*, p. 611.
[d] Figures in parentheses are the adjusted 95% confidence intervals.
[e] Figures in italics are the 95% confidence intervals.
[f] Mantel–Haenszel weighted rate ratio, adjusted for design effects.

CI = 0.54, 0.90), but no reduction was observed for the 0–5-month age group (RR = 0.97; 95% CI = 0.73, 1.29).

Discussion

The data from the studies we have reviewed indicate that supplementation with vitamin A has no consistent overall protective or detrimental effect on pneumonia-specific mortality in children aged between 6 months and 5 years of age. This is in contrast to the demonstrated impact of vitamin A supplementation on all-cause mortality, and on diarrhoea-specific and measles-specific mortality. In all of the studies examined, the impact on pneumonia mortality was different from that on all-cause mortality. Although

Table 4: **Impact of vitamin A supplementation on pneumonia-specific mortality among infants**

Study	Vitamin A		Placebo		Rate ratio	Design effect[a]
	No. of deaths	No. of child-years	No. of deaths	No. of child-years		
Age group: 0–5 months						
JUMLA	2	118.2	5	111	0.38	1.416
MADURAI	0	17.5	0	17.8	—	1.329
SARLAHI[b]	28	1 748	28	1 670	0.96	1.187
SUDAN	0	5	0	2.5	—	1.000
VAST-CSS	0	8	0	10	—	2.003
Summary	30	1 896.7	33	1 811.3	0.88 (0.51–1.51)[c]	
Age group: 6–11 months						
JUMLA	5	173.1	7	146.9	0.61	1.416
MADURAI	0	193.4	0	190.8	—	1.329
SARLAHI	12	1 789	11	1 690	1.03	1.187
SUDAN	0	405.5	0	436	—	1.000
VAST-CSS	14	765	8	809	1.85	2.003
Summary	31	3 325.7	26	3 272.5	1.08 (0.57–2.03)	

[a] Empirical design effect; see footnote *a*, p. 611.
[b] Based on the first 16 months' data out of a total of 24 months' follow-up.
[c] Figures in parentheses are the 95% confidence intervals.

Table 5: **Impact of vitamin A supplementation on all-cause mortality among infants**

Study	Vitamin A		Placebo		Rate ratio	Design effect[a]
	No. of deaths	No. of child-years	No. of deaths	No. of child-years		
Age group: 0–5 months						
JUMLA	20	120.2	19	112.9	0.99	1.416
MADURAI	0	17.5	0	17.8	—	1.329
SARLAHI[b]	98	1 748.0	96	1 670.0	0.97	1.187
SUDAN	0	5.0	0	2.5	—	1.000
VAST–CSS	0	8.0	0	10.0	—	2.003
Summary	118	1 884.7	116	1 797.2	0.97 (0.73–1.29)[c]	
Age group: 6–11 months						
JUMLA	24	179.3	41	157.2	0.61	1.416
MADURAI	2	193.4	7	190.8	0.28	1.329
SARLAHI	43	1 789.0	68	1 690.0	0.60	1.187
SUDAN	1	405.5	0	436.0	?	1.000
VAST–CSS	86	765.0	94	809.0	0.97	2.003
Summary	156	3 320.5	210	3 272.7	0.69 (0.54–0.90)	

[a] Empirical design effect; see footnote *a*, p. 611.
[b] Based on the first 16 months' data out of a total of 24 months' follow-up.
[c] Figures in parentheses are the 95% confidence intervals.

the small number of pneumonia deaths makes it unlikely that a significant difference between the impact on pneumonia mortality and that on mortality from other causes can be demonstrated in any individual study, the consistency of this relationship is striking. In the Sudan study, there was a large impact on deaths associated with "shortness of breath" despite the absence of an impact on all-cause mortality. This result however, needs to be interpreted with caution: shortness of breath is a very nonspecific symptom for pneumonia, and accounted for far fewer deaths (<10%) than would be expected to be attributed to pneumonia in such a population.

The lack of impact of vitamin A supplementation on pneumonia-specific mortality was probably not because of misclassification of pneumonia deaths due to problems associated with the measurement instrument (verbal postmortem). The across-studies consistency in the impact on specific causes of death, despite possible differences in the assignment of cause of death in the various studies, makes this an unlikely explanation for the results. A nonsystematic misclassification of cause of death would be expected to displace the estimate of the impact of supplementation on pneumonia deaths towards that of the impact on all-cause mortality, not towards a rate ratio of unity. This was observed in the SARLAHI study, when a less specific definition of pneumonia-associated deaths was used. Furthermore, similar verbal postmortem instruments have been successfully used in evaluating the impact of other interventions, e.g., pneumonia case management.

The results of this analysis are consistent with those of a previous review of the effectiveness of vitamin A supplementation on all-cause mortality in children over 6 months of age,[c] which also examined the impact on respiratory morbidity and mortality. Six out of the eight field studies included in the last-mentioned review demonstrated a large impact of vitamin A interventions on overall childhood mortality (*18–21, 23, 24*), and a meta-analysis yielded a 23% summary estimate of effect (RR = 0.77; 95% CI = 0.71, 0.84).[c] All the studies that recorded the cause of death showed an impact on deaths due to diarrhoea (summary estimate: RR = 0.71; 95% CI = 0.57, 0.88) and measles (summary estimate: RR = 0.46; 95% CI = 0.22, 0.98), but showed no impact on pneumonia mortality. Similarly, no impact on pneumonia morbidity was demonstrated.

There are insufficient data for infants aged under 6 months to make any judgement about the risk of

[c] See footnote *a*, p. 611.

pneumonia-specific mortality among this age group. The meta-analysis carried out by Beaton et al. derived a 23% summary estimate of the impact on all-cause mortality in young infants (RR = 0.77; 95% CI = 0.38, 1.54), but noted that the data were scanty and the result was not statistically significant.[d] This is in contrast to the estimated impact on young infants from our analysis. In the meta-analysis performed by Beaton et al., the age attribution of deaths for the MADURAI study (which contributed 425 out of the 986 young infants used in the analysis) was based on age at entry into the trial. For the present meta-analysis, the principal investigators agreed to re-examine the data, and re-analysed the findings based on the actual age at death, as in the protocol. Furthermore, valuable additional data on young infants became available from one of the mortality studies (SARLAHI). In our analysis, the impact on all-cause mortality among 6–11-month-olds was similar to that among older children, but the limited data available from children aged under 6 months who were supplemented with 50 000 or 100 000 IU of vitamin A did not suggest the same protective effect on all-cause mortality in this age group. Pneumonia is the largest contributor to deaths among under-6-month-olds, and the absence of an impact on pneumonia for this age group might provide an explanation for the apparent lack of an impact of vitamin A supplements on all-cause mortality among young infants.

The finding that vitamin A supplementation reduces the risk of death due to diarrhoea and measles, but not deaths due to nonmeasles-associated pneumonia is somewhat surprising. Histopathological evidence suggests that the epithelial changes following vitamin A depletion are more marked in the respiratory tract than in the gastrointestinal tract (*1*). It is also inconsistent with the findings of observational studies that children who were vitamin-A deficient had an increased risk of respiratory morbidity (*10–12*). Furthermore, a strong relationship between VAD and severity of respiratory infections has been demonstrated in clinical studies: administering vitamin A to children with measles reduces the duration and severity of illness, the incidence of complications, case fatality rates, and subsequent morbidity from ARI (*13–16*). Vitamin A supplementation also has had a significant positive impact on respiratory infections among some high-risk groups, e.g., low-birth-weight infants (*27*) and children with a history of frequent respiratory illness (*28*).

JUMLA is the only study in the present meta-analysis that reported a reduction in the incidence of pneumonia following vitamin A supplementation, but it is significant that including or excluding the data from JUMLA did not significantly alter the summary estimate of the impact on pneumonia incidence: the ratio remained close to unity. It appears therefore that vitamin A supplementation has no overall impact on pneumonia incidence, as defined by cough and a measured increase in respiratory rate using age-specific cut-offs, or by maternally reported symptoms. This is consistent with the absence of an impact on pneumonia mortality.

The results from the MORVITA and DELHI studies indicate, however, a possible increase in the risk of ARI symptoms among children receiving vitamin A. In the HAITI study, the 2-week prevalence of respiratory symptoms, such as cough, rhinitis and rapid breathing, was slightly higher among children receiving vitamin A compared with those receiving placebo (*25*). In the meta-analysis, four out of the nine studies that contributed data on the prevalence of coughing showed a 5–10% excess of coughing among the vitamin-A-supplemented group. In view of the high incidence of ARI morbidity in infancy, such small increases in risk could correspond to a large population impact, and these results therefore merit further study.

Our findings have important implications for the safety and efficacy of two proposed approaches to vitamin A supplementation in young children in areas where xerophthalmia is a public health problem — supplementation linked with vaccination contacts and with clinic visits for illness. Despite the apparent lack of an impact on pneumonia morbidity and mortality, the accumulated data indicate that there is a net benefit to giving vitamin A supplements to children aged ≥6 months. Although pneumonia makes a very significant contribution to the mortality burden in this age group, there are other causes of death, such as measles and diarrhoea, which also contribute to the mortality burden, and vitamin A has proven efficacy in reducing such deaths. In areas where VAD is a significant public health problem, vitamin A supplements should be given to children aged ≥6 months either through community-based distribution programmes or through contacts with the health service. Opportunities for supplementation through the health services include well-baby-clinic visits, sick-child visits, and EPI contacts (the WHO–EPI 6-month plus recommendations), or special periodic mass supplementation exercises. Vitamin A has also been shown to reduce measles-associated pneumonia deaths and should be administered to children with measles.

[d] See footnote *a*, p. 611.

Résumé

Interventions possibles en vue de la prévention de la pneumonie infantile dans les pays en développement: méta-analyse des résultats d'essais pratiques visant à évaluer l'effet de la supplémentation en vitamine A sur la morbidité et la mortalité associées à la pneumonie

Cet article étudie l'effet de la distribution de suppléments de vitamine A sur la morbidité et la mortalité associées à la pneumonie grâce à une méta-analyse des données recueillies jusqu'en janvier 1993 dans 12 essais pratiques à grande échelle menés dans sept pays. Cette étude s'inscrit dans un projet plus large d'évaluation des possibilités de prévention de la pneumonie chez l'enfant.

Cinq études ont fourni des informations relatives à l'effet des suppléments de vitamine A sur l'incidence des pneumonies. Si l'on considère ces études individuellement, une seule (Jumla, Népal) révèle un effet significatif (taux relatif (RR) = 0,77). Pour les autres études, les taux relatifs varient de 0,92 à 1,14. Globalement, les données n'indiquent aucun effet positif ou négatif sur l'incidence des pneumonies. Le taux relatif global calculé pour l'ensemble des études est de 0,95 (intervalle de confiance (IC à 95% = 0,89–1,01), ou 0,99 (IC à 95% = 0,92–1,06) si l'on exclut les données de l'étude de Jumla.

Dans les cinq études où l'on trouve des données sur les causes de mortalité, le risque relatif combiné de mortalité par pneumonie est de 0,98 (IC à 95% = 0,75–1,28). Ce résultat contraste nettement avec l'effet appréciable des suppléments de vitamine A sur la mortalité toutes causes confondues (RR combiné = 0,77; IC à 95% = 0,71–0,84) et avec leur effet démontré sur la mortalité due à la diarrhée et à la rougeole.

Aucune différence en fonction de l'âge n'a été mise en évidence en ce qui concerne l'effet sur la mortalité attribuable à la pneumonie. Etant donné que la majorité des décès par pneumonie, soit environ 75%, surviennent dans la première année de la vie, il a été procédé à un examen détaillé de toutes les causes de mortalité chez les nourrissons pour pallier la rareté des données sur la mortalité par pneumonie dans cette tranche d'âge. La réduction de la mortalité entre 6 et 11 mois correspond à celle observée chez les enfants plus âgés (RR = 0,69; IC à 95% = 0,54 à 0,90), mais il n'y a eu aucune réduction dans la tranche de 0 à 5 mois (RR = 0,97; IC à 95% = 0,73–1,29). L'absence d'impact des suppléments de vitamine A au cours des six premiers mois de la vie est en accord avec l'absence d'effet que nous avons observée sur les décès dus à la pneumonie, principale cause de mortalité dans cette tranche d'âge.

S'il est prouvé que l'administration de suppléments de vitamine A réduit le risque de décès chez les enfants âgés de six mois et plus, elle est inefficace pour la prévention des décès dus à la pneumonie et ne présente aucun avantage démontré dans la petite enfance. D'autres méthodes de prévention sont nécessaires dans ce cas.

References

1. **Wolbach SB, Howe PR.** Tissue changes following deprivation of fat-soluble vitamin A. *Journal of experimental medicine*, 1925, **42**: 753–777.
2. **Blackfan KD, Wolbach SB.** Vitamin A deficiency in infants: a clinical and pathological study. *Journal of pediatrics*, 1933, **3**: 679–706.
3. **Wong YC, Buck RC.** An electron microscopic study of metaplasia of the rat trachea epithelium in vitamin A deficiency. *Laboratory investigation*, 1971, **24**: 55–66.
4. **Mohanram M, Reddy V, Mishra S.** Lysozyme activity in plasma and leucocytes in malnourished children. *British journal of nutrition*, 1974, **32**: 313–316.
5. **Chandra RK.** Increased bacterial binding to respiratory epithelial cells in vitamin A deficiency. *British medical journal*, 1988, **297**: 834–835.
6. **Ross AC.** Vitamin A status: relationship to immunity and the antibody response. *Proceedings of the Society for Experimental Biology and Medicine*, 1992, **200**: 303–330.
7. **Semba RD et al.** Depressed immune response to tetanus in children with vitamin A deficiency. *Journal of nutrition*, 1992, **122**: 101–107.
8. **Friedman A, Sklan D.** Antigen-specific immune response impairment in the chick as influenced by dietary vitamin A. *Journal of nutrition*, 1989, **119**: 790–795.
9. **Bhaskaram C, Reddy V.** Cell-mediated immunity in iron and vitamin deficient children. *British medical journal*, 1975, **3**: 522.
10. **Bloem MW et al.** Mild vitamin A deficiency and risk of respiratory tract diseases and diarrhoea in preschool and school children in Northeastern Thailand. *American journal of epidemiology*, 1990, **131**: 332–339.
11. **Milton RC, Reddy V, Naidu AN.** Mild vitamin A deficiency and childhood morbidity — an Indian experience. *American journal of clinical nutrition*, 1987, **46**: 827–829.
12. **Sommer A, Katz J, Tarwotjo I.** Increased risk of respiratory disease and diarrhoea in children with pre-existing vitamin A deficiency. *American journal of clinical nutrition*, 1984, **40**: 1090–1095.
13. **Coutsoudis A, Broughton M, Coovadia HM.** Vitamin A supplementation reduces measles morbidity in young African children: a randomized, placebo-

controlled, double-blind trial. *American journal of clinical nutrition*, 1991, **54**: 890–895.
14. **Hussey GD, Klein M.** A randomized, controlled trial of vitamin A in children with severe measles. *New England journal of medicine*, 1990, **323**: 160–164.
15. **Barclay AJG, Foster A, Sommer A.** Vitamin A supplements and mortality related to measles: a randomised clinical trial. *British medical journal*, 1987, **294**: 294–296.
16. **Ellison JB.** Intensive vitamin therapy in measles. *British medical journal*, 1932, **2**: 708–711.
17. **The World Bank.** *World development report 1993: investing in health.* New York, Oxford University Press, 1993.
18. **Daulaire NMP et al.** Childhood mortality after a high dose of vitamin A in a high risk population. *British medical journal*, 1992, **304**: 207–210.
19. **West KP Jr et al.** Efficacy of vitamin A in reducing preschool child mortality in Nepal. *Lancet*, 1991, **338**: 67–71.
20. **Muhilal et al.** Vitamin A-fortified monosodium glutamate and health, growth, and survival of children: a controlled field trial. *American journal of clinical nutrition*, 1988, **48**: 1271–1276.
21. **Rahmathullah L et al.** Reduced mortality among children in Southern India receiving a small weekly dose of vitamin A. *New England journal of medicine*, 1990, **323**: 929–935.
22. **Vijayaraghavan K et al.** Effect of massive dose vitamin A on morbidity and mortality in Indian children. *Lancet*, 1990, **336**: 1342–1345.
23. **Sommer A et al.** Impact of vitamin A supplementation on childhood mortality: a randomised controlled community trial. *Lancet*, 1986, **1**: 1169–1173.
24. **Ghana VAST Study Team.** Vitamin A supplementation in northern Ghana: effects on clinic attendances, hospital admissions, and child mortality. *Lancet*, 1993, **342**: 7–12.
25. **Stansfield SK et al.** Vitamin A supplementation and increased prevalence of childhood diarrhoea and acute respiratory infections. *Lancet*, 1993, **342**: 578–581.
26. **Herrera HG et al.** Vitamin A supplementation and child survival. *Lancet*, 1992, **340**: 267–271.
27. **Shenai J et al.** Clinical trial of vitamin A supplementation in infants susceptible to bronchopulmonary dysplasia. *Journal of pediatrics*, 1987, **111**: 269–277.
28. **Pinnock CB, Douglas RM, Baddock N.** Vitamin A status in children who are prone to respiratory tract infections. *Australian pediatric journal*, 1986, **22**: 95–99.