Childhood mortality after a high dose of vitamin A in a high risk population

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Abstract

***Objectives*—To determine whether a single high dose of vitamin A given to all children in communities with high mortality and malnutrition could affect mortality and to assess whether periodic community wide supplementation could be readily incorporated into an ongoing primary health programme.**

***Design*—Opportunistic controlled trial.**

***Setting*—Jumla district, Nepal.**

***Subjects*—All children aged under 5 years; 3786 in eight subdistricts given single dose of vitamin A and 3411 in remaining eight subdistricts given no supplementation.**

***Main outcome measures*—Mortality and cause of death in the five months after supplementation.**

***Results*—Risk of death for children aged 1-59 months in supplemented communities was 26% lower (relative risk 0·74, 95% confidence interval 0·55 to 0·99) than in unsupplemented communities. The reduction in mortality was greatest among children aged 6-11 months: death rate (deaths/1000 child years at risk) was 133·8 in supplemented children and 260·8 in unsupplemented children (relative risk 0·51, 0·30 to 0·89). The death rate from diarrhoea was also reduced (63·5 supplemented *v* 97·5 unsupplemented; relative risk 0·65, 0·44 to 0·95). The extra cost per death averted was about $11.**

***Conclusion*—The results support a role for Vitamin A in increasing child survival. The supplementation programme was readily integrated with the ongoing community health programme at little extra cost.**

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Introduction

Vitamin A deficiency has been suggested as a possible risk factor for childhood illness and death. Studies from Indonesia, India, and the lowlands of Nepal indicated that wide scale supplementation with vitamin A reduced child mortality in deficient populations,[1-4] though a recent Indian study found no beneficial effect.[5] These programmes were carried out as large single intervention research studies, and it is not clear whether vitamin A supplementation could be incorporated into ongoing primary health care services without adding considerably to the cost.

The benefits of routine vitamin A supplementation in preventing blindness are well documented, and supplementation is warranted wherever substantial xerophthalmia is found.[6] During a three year intervention trial of management of pneumonia in Jumla district, Nepal,[7] eye signs suggestive of severe xerophthalmia in the period preceding death were often reported in the more than 2000 verbal postmortem reports. Despite earlier studies of xerophthalmia in Nepal reporting that vitamin A deficiency was not a major problem in mountainous areas,[8] this observation suggested that serious deficiency might exist.

At the end of the pneumonia trial we initiated routine periodic vitamin A supplementation for all children under 5 years. Because new field implementation systems were required and immediate full coverage was impracticable the programme was phased in over six months, resulting in an initial period in which only half the children were given supplementation. We assessed the difference in mortality between supplemented and unsupplemented populations and analysed the cost and impact on the health programme.

Subjects and methods

Jumla district lies in a remote mountainous region of northwestern Nepal. The district's population is about 80 000, with 12 000 children under 5 years. It is one of the poorest and most medically underserved areas of the country. Child mortality is extremely high, with an infant mortality of 189 deaths per 1000 live births and a death rate in children aged 1-4 years of 52 per 1000 children per year.[7] Malnutrition is prevalent, and 26% of children aged 1-4 years have arm circumferences indicating substantial malnutrition (<12·5 cm)[7,9]; exclusive breast feeding up to 6 months is universal. In a survey of 3651 children under 5 years, active xerophthalmia was detected in 13·2%[10]; xerophthalmia among infants was 1·5%, which is high for this age group. Diarrhoea and pneumonia are the leading causes of death in children after the first week of life.[7]

Full registration of vital events (births, deaths, and disease) had been done in 16 subdistricts of Jumla for the past three years. The subdistricts were geographically, nutritionally, and economically similar. We randomly selected by card eight of the 16 subdistricts for vitamin A supplementation. The other eight subdistricts served as concurrent observation areas; there was no placebo or blinding. During three weeks in May-June 1989 a single high dose capsule of retinol palmitate (with vitamin E) was given to all children in the selected districts. The standard dose was 200 000 IU vitamin A for children aged 12-59 months, 100 000 IU for infants aged 6-11 months, and 50 000 IU for infants under 6 months.

Vitamin A was given by nine local lay health workers from the ongoing pneumonia case management programme. These workers visited each household, explained the purpose of vitamin A supplementation to each family, obtained informed consent, and gave the vitamin capsule to each child under 5 years. All households with absent children were revisited within two weeks to assure maximum coverage; no capsules were left behind to be taken unsupervised. Only neonates with jaundice were excluded from coverage. To prevent confusion and the possibility of multiple

dosing, after this three week campaign vitamin A capsules were not made available to field workers until the next scheduled round.

Routine detection and treatment of pneumonia, as carried out over the previous three years, took place throughout all communities during the observation period. There was no difference between subdistricts in the availability or intensity of health services. No nutritional services other than the vitamin A supplementation were available from any source.

Registration of vital events and verbal postmortem reports for all deaths were continued in the 16 subdistricts by staff totally separate from those implementing the vitamin A programme. Earlier periodic assessments of the system for registering vital events had found better than 99% recording of events and a high level of reliability for the verbal postmortem instrument.[7] All children born before June 1989 and all deaths in children aged 1-59 months during June to October were included in the analysis. Infants less than 1 month of age were excluded as the supplementation campaign did not include repeated follow up to reach births occurring during the observation period. Definition of group was based on the conservative standard of intention to treat, so that all children dying in subdistricts allocated to supplementation were regarded as supplemented regardless of whether the child had actually received vitamin A. Causes of death based on verbal postmortem reports were blindly reviewed.

TABLE I—*Baseline characteristics of study populations*

	No (%) of children in communities given vitamin A (n=3786)	No (%) of children in communities not given vitamin A (n=3411)
Sex:		
Male	1976 (52·2)	1743 (51·1)
Female	1810 (47·8)	1668 (48·9)
Age (months):		
1-15	547 (14·4)	511 (15·0)
6-11	357 (9·4)	329 (9·6)
12-23	836 (22·1)	766 (22·5)
24-35	724 (19·1)	631 (18·5)
36-47	750 (19·8)	628 (18·4)
48-59	572 (15·1)	546 (16·0)

TABLE II—*Mortality in children 1-59 months old before start of vitamin A supplementation*

	Supplemented subdistricts		Unsupplemented subdistricts	
	No of deaths	Death rate*	No of deaths	Death rate*
Deaths during 24 months before study	506	73·5	429	70·2†
Deaths during June-October, 1987 and 1988	348	121·6	281	110·6†

*Deaths per 1000 child years at risk. †Differences not significant.

TABLE III—*Mortality during June-October 1989 in children in subdistricts allocated to vitamin A supplementation and those in unsupplemented subdistricts*

	Supplemented subdistricts			Unsupplemented subdistricts			
	No of deaths	Child years at risk	Death rate*	No of deaths	Child years at risk	Death rate*	Relative risk (95% confidence interval)
Age at death (months):							
1-59	138	1480·1	93·2	167	1323·0	126·2	0·74 (0·55 to 0·99)
1-5	20	120·2	166·4	19	112·9	168·3	0·99 (0·41 to 2·41)
6-11	24	179·3	133·8	41	157·2	260·8	0·51 (0·30 to 0·89)
12-23	62	345·9	179·2	71	320·9	221·3	0·81 (0·53 to 1·23)
24-35	19	302·7	62·8	22	270·8	81·3	0·77 (0·39 to 1·51)
36-47	11	281·0	39·1	11	237·7	46·3	0·85 (0·23 to 3·06)
48-59	2	251·0	8·0	3	223·5	13·4	0·59 (0·08 to 4·21)
Sex:							
Male	71	774·8	91·6	86	676·1	127·2	0·72 (0·48 to 1·08)
Female	67	705·3	95·0	81	646·9	125·2	0·76 (0·48 to 1·19)

*Deaths per 1000 child years at risk, unstandardised.

We used methods described by Breslow and Day[11] to estimate the mortality in the supplemented and unsupplemented districts and the person years (PYRS) software package[12] to compute child years at risk. The death rate was calculated as the deaths per 1000 child years at risk. We also computed death rates by sex, by age at death, and by primary cause of death. The point estimates and 95% confidence intervals for relative risk of mortality for vitamin A supplemented versus unsupplemented children were obtained from a Poisson regression analysis of deaths and aggregate person years at risk in each subdistrict, incorporating variance overdispersion. This model, which uses subdistrict as the unit of analysis, takes account of clustering due to randomisation by subdistrict rather than by child[13,14]; the effect of clustering is reflected in an overdispersion parameter, which results in an increase in the width of the usual Poisson confidence intervals.

Results

The eight supplemented subdistricts had a total of 3786 children aged under 5 at the start of observation, the eight unsupplemented subdistricts had a total of 3411 children; the baseline composition in age and sex were virtually identical (table I). Over the past two years the supplemented subdistricts had shown slightly higher mortality than the unsupplemented, but the difference was small and not significant (table II). Seasonal variation in mortality was high, related to overall food deficit and the high rate of diarrhoeal disease transmission during the summer, and similar between the two sets of subdistricts.

During the supplementation campaign 3345 (88%) of the 3786 eligible children received vitamin A. There were no reported refusals, and a child's extended absence from the home was the principal reported reason for failure to give vitamin A. All children were followed up as part of the routine pneumonia case management programme, and about 2% of those who received vitamin A supplementation were reported to have experienced vomiting, fever, or diarrhoea within a few days after receiving vitamin A. However, as there is a high prevalence of gastroenteritis and diarrhoea in the summer, these symptoms could not be clearly attributed to vitamin A. There were no reported serious toxic reactions, even among very young infants.

During June-October 1989 the relative risk of death among the supplemented population compared with the unsupplemented population was 0·74 (95% confidence interval 0·55 to 0·99, $p<0·05$) for a 26% reduction in childhood mortality among the supplemented population after a single dose of vitamin A (table III). The effect of clustering on the analysis was to increase the width of the confidence interval by 19% over the usual Poisson confidence interval. In all, 138 deaths occurred in the supplemented group and 167 in the unsupplemented group, giving death rates of 93 and 126 deaths per 1000 child years at risk, respectively. Differences in mortality could be seen within a few days of supplementation but continued to widen with time (figure).

The effect of supplementation seemed to be greatest among children aged 6 to 11 months (relative risk 0·51, 95% confidence interval 0·30 to 0·89), but was also apparent in all older age groups. Among infants aged 1-5 months, the point estimate of relative risk of death was 0·99 but the confidence interval was wide (0·41 to 2·41). The effect of supplementation on mortality was similar for both sexes. Boys and girls in the supplemented population showed a relative risk of death of 0·72 and 0·76, respectively compared with the unsupplemented population.

Analysis of causes of death according to verbal postmortem reports indicated that the greatest decrease

TABLE IV—*Aggregated cause specific mortality among children 1-59 months old*

Primary cause	Supplemented subdistricts: No of deaths	Supplemented subdistricts: Death rate*	Unsupplemented subdistricts: No of deaths	Unsupplemented subdistricts: Death rate*	Relative risk (95% confidence interval)
Diarrhoea†	94	63·5	129	97·5	0·65 (0·44 to 0·95)
Pneumonia	18	12·2	17	12·9	0·95 (0·38 to 2·33)
Measles	3	2·0	4	3·0	0·67 (0·07 to 6·37)
Other‡	23	15·5	17	12·8	1·21 (0·56 to 2·62)

*Cause-specific death rate per 1000 child years at risk.
†Includes nine deaths due to diarrhoea with underlying measles.
‡Includes three deaths due to injuries and 10 due to primary malnutrition.

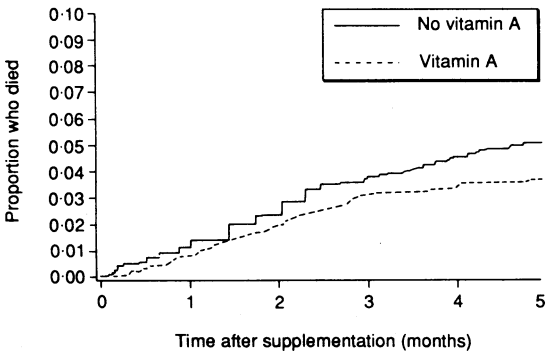
in cause specific mortality was observed in deaths attributed to diarrhoea (relative risk 0·65, 95% confidence interval 0·44 to 0·95) (table IV). Additionally, decreases were noted in deaths attributed to measles (0·67, 0·07 to 6·37) and to pneumonia (0·95, 0·38 to 2·33), but these causes were responsible for only 2% and 11% of deaths respectively, so the confidence intervals were wide. There was no apparent benefit for mortality from other causes (1·21, 0·56 to 2·62).

Discussion

A single high dose of vitamin A given to all children aged under 5 years significantly reduced the risk of death among a malnourished population with a high mortality and high prevalence of xerophthalmia. Our data indicate that during the five month observation period one death was averted for every 55 vitamin A capsules administered. This supports the positive findings of several of the earlier studies[1-4] and indicates that vitamin A supplementation is appropriate in child survival programmes.

The size of the protective effect in infants aged 6-12 months (49% reduction in mortality) was greater than has been reported by other studies[3,4] and may reflect the harsh nutritional environment of infants in Jumla. Foods rich in vitamin A are not a part of the Jumla diet, and mothers commonly report night blindness during pregnancy, suggesting that even gestational and lactational stores may be limited. Weaning traditionally begins at 6 months, resulting in a decrease of vitamin A from breast milk. These factors may also explain the unusual finding of a 1·5% rate of active xerophthalmia among infants.[10]

Supplementation of vitamin A starting in early infancy may be warranted among similar populations with high levels of xerophthalmia and general malnutrition. We found no significant adverse consequences associated with giving high doses to infants. The power of our study was not sufficient to determine benefit for infants aged less than 6 months; the point estimate of relative risk was 0·99 for this age group but the lower limit of the 95% confidence interval was 0·41, so we cannot rule out a sizable effect. As earlier studies have indicated that the effect of supplementation may be cumulative and increase over time,[4] the effect on this age group may not become apparent until the population has been followed for longer.



Proportions of children who died during follow up according to vitamin A supplementation

The death rate observed in the unsupplemented population was consistent with data collected during the same months in the previous two years, which makes it unlikely that factors unrelated to the programme significantly affected mortality in unsupplemented communities. The low mortality from measles, the commonest cause of epidemics in this population, also supports this. Observer (Hawthorne) effect is not likely to have contributed to the difference in mortality as apart from the one visit to give vitamin A the amount of contact with health workers did not differ between the two groups and all households throughout the district continued to be visited every two weeks for detection and treatment of pneumonia.

VITAMIN A AND DISEASE

Earlier studies have reported an association between vitamin A status and the risk of illness or death from specific infections, notably diarrhoea, pneumonia, and measles.[15-18] Our study strongly supports the association with deaths from diarrhoeal diseases but the effect on deaths from pneumonia and measles was less clear. The predominant influence on deaths from diarrhoeal disease, both in terms of absolute numbers and in percentage reduction, is not surprising given the close relation between diarrhoea and malnutrition.[19] This finding indicates that if a sustained year round vitamin A supplementation programme is not feasible in malnourished populations with a high child mortality vitamin A would best be targeted at the period preceding seasons in which morbidity and mortality from diarrhoea are at their peak.

Even though an equivalent impact on mortality from pneumonia could not be clearly determined due to the wide confidence interval, a smaller proportional effect on mortality from pneumonia is consistent with the age related reduction in mortality we observed. Registration of vital events among this population has shown that most deaths from pneumonia occur before the age of 6 months,[7] the age group in which a reduction in mortality after vitamin A supplementation was not evident. Effect on mortality from pneumonia may also have been reduced by the fact that an active programme of antibiotic management of pneumonia was ongoing throughout both the supplemented and unsupplemented population, minimising deaths from this cause. The number of deaths from measles during the observation period was too small to give a clear indication of effect; generally measles epidemics are not common in Jumla during the summer.

Both regular low dose vitamin A supplementation[2,3] and periodic (four to six monthly) high dose supplementation[1,4] have been found to reduce mortality in childhood. The effect of low dose supplementation indicates the potential impact of including more foods rich in vitamin A in the diet, but fundamental behavioural change at the household level can be accomplished only over several years, during which time children would continue to die needlessly. We have shown that periodic supplementation is effective, if necessary even on an emergency campaign basis, and can be implemented in even the most underserved populations.

IMPLEMENTING THE PROGRAMME

We found that vitamin A supplementation did not overburden field staff and that it could be readily incorporated into the existing community based health services that our programme provides to the children of Jumla. Supplementation of all children aged 5 has been carried out throughout the district from late 1989 until the present. This approach should be replicable even where primary health care services are rudimentary.

The extra cost of the supplementation programme

(capsules, staff, and management time) was less than $0.20 per dose. Based on our calculation of deaths averted, this indicates a total marginal cost of less than $11 per death averted, making vitamin A supplementation a highly cost effective strategy for increasing child survival which should be sustainable over an extended period. Of course our estimate of cost per death averted is particularly low because of the extremely high underlying mortality and vitamin A deficiency among our population and because of the existence of a viable delivery system on which to add vitamin A distribution; these factors will vary in other settings.

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Stability of essential drugs during shipment to the tropics

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Abstract

***Objective*—To determine whether present methods of international transport of essential drugs by sea adversely affect their quality.**

***Design*—Controlled longitudinal study of drug shipments sent by sea from Unicef in Copenhagen to Lagos; to Mombasa and by land to Kampala; and to Bangkok. 11 essential drugs were stored in four locations on board the ships.**

***Setting*—Main shipping routes from Unicef, Copenhagen, to tropical countries.**

***Main outcome measures*—Temperature and relative humidity in the test packs during the journey. Amount of active ingredient in the drugs before and after shipment.**

***Results*—Temperatures recorded within the test packs range from −3·5°C to 42·4°C and were 3-12°C higher than the ambient temperature. Relative humidity within the packs ranged from 20% to 88%. Differences between the locations on board were negligible. Ergometrine injection, methylergometrine injection, and retinol capsules lost 1·5-5·8% of their activity. Ampoules of ergometrine showed a large variation in the amount of active ingredient after shipment, with three of 80 samples having concentrations 60% below those stated. Ampicillin, benzylpenicillin, phenoxymethylpenicillin, and tetracycline were not affected by transport.**

***Conclusions*—Drugs were exposed to a much higher temperature and humidity than is recommended by the manufacturer, especially in tropical harbours and during inland transport. Except for ergometrine and methylergometrine the transport would not affect clinical effectiveness.**

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Introduction

In 1987 Unicef sent over $30 million worth of essential drugs to tropical countries.[1] The stability of medicines distributed and used in hot and humid climates can pose serious problems, but stability studies and storage guidelines usually refer to temperate climates and therefore may not be relevant in extreme climatic conditions.[2] Few studies have described the influence of tropical storage conditions on the quality of medicines.[3] The World Health Organisation and Unicef therefore carried out a joint study on the stability of essential drugs during international transport.

Materials and methods

We used three criteria to select drugs for the study. The first criterion was an indication from WHO accelerated stability tests[4] or other studies[5-8] that the active substance or the drug product could be unstable in tropical climates. The other criteria were that Unicef has a high turnover of the drug in volume or in value and in medical relevance. Eleven drugs were selected. All samples were taken from normal Unicef stock, and