Child Morbidity and Mortality following Vitamin A Supplementation in Ghana: Time since Dosing, Number of Doses, and Time of Year

ABSTRACT

Objectives. The impact of large-dose vitamin A supplementation given at intervals of 4 months on child mortality and morbidity was examined according to the time interval since dosing, number of doses received previously, and time of year.

Methods. Two double-blind, randomized, placebo-controlled trials of large doses of vitamin A administered at intervals of 4 months were conducted in adjacent populations in northern Ghana.

Results. While vitamin A supplementation significantly reduced the overall incidence of severe illnesses (especially diarrhea with dehydration), clinic attendances, hospital admissions, and mortality, there was no evidence that the impact of each dose of vitamin A was related to the number of doses the child had received previously. There was no evidence that the effectiveness of the supplement waned over the 3 to 5 months between doses. The impact on mortality did not differ significantly by the month in which the supplement had been given.

Conclusions. In the study population, there was no evidence that an interval between doses of less than 4 months would have had a greater impact on severe morbidity or mortality, and the effectiveness of supplementation did not vary by time of year. (*Am J Public Health.* 1995;85: 1246–1251)

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Introduction

Several randomized controlled trials have shown that increased vitamin A intake can substantially reduce both child mortality[1–6] and severe morbidity.[1,7,8] This has increased the priority being given to improving the vitamin A intake of young children in areas where vitamin A deficiency is prevalent.[9–11] There are three main strategies for achieving this goal that have been used either individually or in various combinations: supplementation, food fortification, and dietary modification (through the increased production, availability, and consumption of foods rich in vitamin A).[12] Although both food fortification and dietary modification strategies may prove to be more cost-effective than supplementation in the long term, prophylactic supplementation linked to routine contacts with health services has been estimated to be one of the most cost-effective potential child health interventions in areas where vitamin A deficiency is a problem of public health importance.[13]

Most authorities recommend prophylactic doses of 100 000 IU retinol for children 6 to 11 months of age and doses of 200 000 IU for children 12 months of age and older.[14] There has been no clear agreement on the most suitable dosing interval, but a span of 4 to 6 months has generally been recomended.[14–16] A decision on the appropriate dosing interval is of great importance for health programs, since too short an interval would unnecessarily increase program costs and too long an interval could substantially dilute the impact.

The available evidence on the best dosing interval has been reviewed by West and Sommer[17]; their review included theoretical calculations, studies of the effect of a single large dose of vitamin A on a child's subsequent serum retinol level, and studies of the protective efficacy of vitamin A supplements against xerophthalmia.[17] They concluded that "the period during which elevated serum retinol levels can be maintained in children who initially exhibit low or marginal vitamin A status is highly variable, with optimistic estimates ranging from 8 to 42 weeks" and protection against xerophthalmia lasting for at least 4 months.[17]

It is not known whether the beneficial impact on morbidity and mortality of repeated vitamin A supplements given at 4-month intervals either increases or decreases in relation to the number of doses the child has received previously. Furthermore, it is possible that the size of the impact might vary according to the time of year in which the supplement has been given. This could occur either because of seasonal variations in the dietary vitamin A intake of the children or because of differential effects of supple-

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mentation on major, seasonal causes of death (such as diarrhea, measles, acute respiratory infections, and malaria). If the beneficial impact were largely confined to doses given at certain times of the year, programs could focus their resources on delivery of supplements at those times, with substantial logistic and cost savings.

We have previously reported the main results of two randomized, double-blind, placebo-controlled trials designed to evaluate the impact of large doses of vitamin A administered at 4-month intervals on childhood mortality (the Vitamin A Supplementation Trials Survival Study) and morbidity (the Vitamin A Supplementation Trials Health Study) in northern Ghana.[1,7] In summary, vomiting (rate ratio [RR] = 0.87), anorexia (RR = 0.85), dehydrating diarrhea (RR = 0.85), clinic attendances (RR = 0.88), hospital admissions (RR = 0.62), and deaths (RR = 0.81) were all significantly less frequent in the children receiving vitamin A supplementation.[1,7] There was strong evidence that supplementation had reduced mortality due to acute gastroenteritis (RR = 0.66, 95% confidence interval [CI] = 0.47, 0.92) but no definite evidence of reductions in deaths due to any of the other three major causes of death: measles (RR = 0.82, 95% CI = 0.48, 1.40), acute respiratory infections (RR = 1.00, 95% CI = 0.61, 1.64), and malaria (RR = 1.03, 95% CI = 0.74, 1.43).[1] No significant differences were found between children in the vitamin A and placebo groups in mean daily prevalence of less severe diarrhea, acute respiratory infections, or any of the other symptoms or conditions inquired about.[7]

The trials have provided the opportunity to evaluate the impact of large-dose vitamin A supplementation at intervals of 4 months on childhood mortality and morbidity according to the time since the most recent dose was received and the number of doses of vitamin A that the child had previously received within the trial. The impact on mortality according to the time of year at which the supplement was given was also examined.

Methods

Full details of the study populations and the data collection methods of the two trials have been given elsewhere.[1] A summary of the design of the two trials is provided in Table 1.

TABLE 1—The Design of the Vitamin A Supplementation Trials Survival and Health Studies, Ghana

	Survival Study (n = 21 906)	Health Study (n = 1455)
Age range at entry to trial, mo	6–90	6–57
Unit of random treatment allocation	185 geographical clusters (mean of 51 children per cluster)	Individual child
Vitamin A dose (retinol equivalents), mg		
6–11 mo	30	30
12+ mo	60	60
Interval between doses of vitamin A or placebo, mo	4	4
Follow-up		
Interval between visits, wks	17	1
Duration, mo	24	12
Start of follow-up	Sept–Dec 1989	June–August 1990
Child-years of follow-up, no.	33 287	1185

Study Populations

The two trials were carried out in adjacent rural populations of the Kassena-Nankana District of Ghana, which borders Burkina Faso to the north. The area has a sub-Sahelian climate. Xerophthalmia was present in 0.7% and 1.5% of the children in the Survival Study and Health Study populations, respectively, but the proportions of children with serum retinol levels below 0.70 μmol/L, indicating either moderate or severe biochemical vitamin A deficiency, were substantial (57% in the Survival Study population and 73% in the Health Study population).

All children living in the two study areas were eligible to enter the trials at any of the 4-month dosing points if they had reached the age of 6 months. Children born from 1984 onward were included in the Survival Study; the Health Study restricted admission to children born from 1986 onward. The Survival Study trial was carried out between September 1989 and December 1991, and the Health Study trial was carried out between June 1990 and August 1991. The maximum age of any child at entry into the Survival study was 90 months; the corresponding figure for the Health Study was 57 months.

Treatment Allocation and Dosing

Children 6 months of age or older were randomly allocated to receive either retinol or placebo at each of the subsequent 4-month dosing rounds. Randomization was by geographical cluster in the Survival Study but by individual in the Health Study. The dosing regime was the same in both trials: children 6 to 11 months of age received an oral dose of 30 mg (100 000 IU) retinol equivalent (retinyl palmitate in purified peanut oil) or placebo, while older children received 60 mg (200 000 IU) retinol equivalent or placebo. The placebo was purified peanut oil. Children enrolled at the start of the two trials could receive up to three doses of vitamin A or placebo administered at 4-month intervals in the Health Study or up to six doses in the Survival Study. Children with confirmed xerophthalmia were treated with vitamin A and either not entered into the trial or withdrawn from the trial at the time the diagnosis was made.

Follow-Up

In the Survival Study, the children were visited and given vitamin A or placebo by trained fieldworkers every 4 months for 2 years, in seven survey rounds. Child deaths were identified at the time of the home visits and also through a network of approximately 100 community informants. A total of 21 906 children (11 072 boys, 10 834 girls) entered the Survival Study, and they were followed for an average of 18.2 months.

In the Health Study, children received weekly home visits from fieldwork-

TABLE 2—The Impact of Vitamin A Supplementation on Child Mortality according to Time since Dose Was Received

Days since Dose	Vitamin A Clusters: Child-Years at Risk	Vitamin A Clusters: No. of Deaths	Vitamin A Clusters: Mortality Rate[a]	Placebo Clusters: Child-Years at Risk	Placebo Clusters: No. of Deaths	Placebo Clusters: Mortality Rate[a]	RR[b] for Vitamin A/Placebo (95% CI)
0–29	3 834.2	67	17.4	3 883.0	89	23.7	0.73 (0.52, 1.04)
30–59	3 835.3	94	24.1	3 883.8	116	27.4	0.88 (0.64, 1.21)
60–89	3 833.7	84	23.0	3 881.3	83	23.7	0.97 (0.67, 1.40)
90–119	3 485.0	76	21.5	3 545.4	112	31.6	0.68 (0.50, 0.93)
120–149	744.2	14	16.7	744.9	13	20.4	0.82 (0.33, 2.01)
0–149	15 457.8	335	21.7	15 756.6	413	26.4	0.82* (0.68, 1.00)

Note. Children whose date of death was not known were excluded. RR = rate ratio; CI = confidence interval.

[a]Per 1000 child-years. χ^2 (trend) = 0.019, P = .89.

[b]Cluster-based analysis (unweighted means of the mortality rates in the clusters assigned to this treatment).

*P = .05.

ers who asked the child's mother about the occurrence, on each day of the previous week, of 21 listed signs, symptoms, and conditions; a detailed assessment was made of the severity of any diarrheal or respiratory illnesses reported.[1] Weekly mobile clinics were held within the Health Study area, at which study children were offered a highly subsidized service to encourage their attendance if sick. All study children who attended the clinic were seen by a study physician who recorded their diagnoses and treatment, and those who were admitted to the local district hospital were monitored daily and treated with standard protocols. A total of 1455 children (720 boys, 735 girls) entered the Health Study, and they were followed for an average of 9.8 months.

Data Quality Control

Several methods were used to promote and check on the quality of the data collected in both trials,[1] including close supervision of the interviewers, blind reinterviews, and frequent refresher courses. The resulting data were independently entered onto computers by two clerks to reduce data entry errors; the data were also subjected to detailed range and consistency checks.

Data Processing and Analysis

Foxpro 2.0, SPSS PC+ 5.0, SAS 6.03, and Egret software were used in conducting analyses. Two-tailed significance tests were used throughout, and continuity corrections were applied where appropriate.

The analysis of the impact of supplementation according to the time since the most recent dose was received was restricted, for each 4-month round, to children who received a correct dose of vitamin A or placebo in that particular round. For the assessment of mortality impact within the Survival Study, the period at risk after a dose was defined as the number of days between the child receiving the dose and either the date when the child died or the date of the next dosing. Similarly, within the Health Study, the period at risk was calculated separately for each of three outcomes (the child's first episode of diarrhea with six or more liquid or semiliquid motions, first attendance at the clinic, and first hospital admission) in each round of the study. The risk period was defined as the number of days between the child receiving the dose and (1) the start of the outcome of interest or (2) the point at which the child died, the point at which he or she was reported to have permanently left the study area, or the date of his or her next dosing.

The impact of supplementation was assessed in five 30-day periods after the dose had been received (0 through 29, 30 through 59, 60 through 89, 90 through 119, and 120 through 149 days). The number of events and person-years at risk were calculated separately for each time period and treatment group, leading to period-specific estimates of the vitamin A:placebo rate ratios. A chi-square test for trend[18] was used to examine trends in the vitamin A:placebo rate ratio over time. In addition, Cox proportional hazards regression[19] was used to test the treatment–time interaction by adding the term reflecting treatment multiplied by log time to a proportional hazards model containing only a treatment-effect term and comparing the change in the deviance with a standard chi-square distribution on one degree of freedom.

The impact of supplementation, in terms of the number of doses the child had received, was assessed by allocating each child's follow-up time into different categories according to the previous number of doses he or she had received. Thus, children's follow-up entered the "one dose" category when they received their first dose and ended in this category when they died, were lost to follow-up, or received their second dose. In the last case, their follow-up would then be assigned to the "two dose" category, and so forth. For each of the three morbidity outcomes, only the first event was included, and children's follow-up for that outcome was terminated at the time they first experienced the outcome.

Whether the mortality impact of supplementation differed by the time of year in which the supplement was given was examined for each dosing round within the Survival Study. In rounds 1 and 4, more than 90% of the doses were given in October or November; in rounds 2 and 5, more than 90% were given in February or March; and in rounds 3 and 6, more than 90% were given in June or July. Of the 1970 mm rainfall during the study period from September 1989 to December 1991, 91.1% fell in the "wet season" months of May to October.

Results

Compliance

The average proportions of eligible children successfully dosed at each round were 89.5% and 94.7% in the Survival and Health Studies, respectively, and these figures were similar in the vitamin A and placebo groups. The great majority of the children who missed doses were away from home at the time of dosing. Overall, 8% of children in each trial were lost to follow-up, with approximately equal proportions in each treatment group. Morbidity information was missing for only 5.7% of the weekly home visits in the Health Study (as a result of temporary absences of the study children and/or their mothers), and this amount was equally distributed between the two treatment groups.

TABLE 3—The Impact of Vitamin A Supplementation on Child Morbidity (First Occurrence of Each Outcome per Study Round) according to Time since Dose Was Received

Days since Dose	Severe Diarrhea[a]					Clinic Attendances					Hospital Admissions				
	Vitamin A		Placebo			Vitamin A		Placebo			Vitamin A		Placebo		
	Child-Years	Rate[b]	Child-Years	Rate[b]	RR[c] (95% CI)	Child-Years	Rate[b]	Child-Years	Rate[b]	RR[d] (95% CI)	Child-Years	Rate[b]	Child-Years	Rate[b]	RR[e] (95% CI)
0–29	132.0	1.86	129.9	2.21	0.84 (0.71, 0.98)	133.6	1.93	130.3	2.32	0.83 (0.71, 0.98)	144.2	0.042	143.6	0.056	0.75 (0.26, 2.15)
30–59	116.6	1.39	113.5	1.18	1.18 (0.94, 1.48)	113.8	1.74	109.8	1.74	1.00 (0.82, 1.22)	143.0	0.056	141.9	0.049	1.13 (0.41, 3.13)
60–89	104.3	1.04	102.1	1.19	0.87 (0.67, 1.13)	98.0	1.43	93.9	1.49	0.96 (0.76, 1.21)	140.2	0.064	138.6	0.123	0.52 (0.23, 1.17)
90–119	91.1	0.91	88.3	0.82	1.12 (0.81, 1.53)	85.0	1.01	80.7	1.04	0.97 (0.72, 1.31)	132.1	0.038	129.4	0.046	0.82 (0.25, 2.67)
120–149	7.3	0.41	7.3	0.69	0.60 (0.14, 2.51)	7.4	0.68	6.8	0.74	0.92 (0.27, 3.17)	11.4	0.000	11.0	0.000	. . .
0–149	451.3	1.33	441.1	1.40	0.95 (0.85, 1.06)	437.8	1.56	421.5	1.71	0.92 (0.83, 1.02)	571.0	0.049	564.5	0.067	0.73 (0.45, 1.19)

Note. RR = rate ratio; CI = confidence interval.
[a]Six or more liquid or semiliquid bowel motions on the worst day.
[b]Per 1000 child-years; only the first event within each round of the study was included (see text).
[c]χ^2 (trend) = 1.21, P = .27.
[d]χ^2 (trend) = 1.10, P = .30.
[e]χ^2 (trend) = 0.06, P = .80.

(*See next page for Table 4*)

TABLE 5—The Impact of Vitamin A Supplementation on Child Morbidity (First Occurrence of Each Outcome in the Study) according to Number of Doses Received

No. Doses Received	Severe Diarrhea[a]					Clinic Attendances					Hospital Admissions				
	Vitamin A		Placebo			Vitamin A		Placebo			Vitamin A		Placebo		
	Child-Years	Rate[b]	Child-Years	Rate[b]	RR[c] (95% CI)	Child-Years	Rate[b]	Child-Years	Rate[b]	RR[d] (95% CI)	Child-Years	Rate[b]	Child-Years	Rate[b]	RR[e] (95% CI)
1	173.8	1.59	171.7	1.71	0.93 (0.79, 1.10)	160.3	2.14	159.8	2.24	0.96 (0.83, 1.11)	235.3	0.064	237.0	0.084	0.76 (0.39, 1.48)
2	109.3	0.76	105.0	0.78	0.97 (0.72, 1.32)	90.1	0.86	85.5	0.86	1.00 (0.73, 1.38)	189.2	0.037	189.5	0.084	0.44 (0.18, 1.07)
3	77.3	0.46	69.5	0.30	1.54 (0.90, 2.64)	56.4	0.85	53.0	0.73	1.16 (0.76, 1.77)	148.9	0.013	144.3	0.021	0.65 (0.11, 3.87)
1–3	360.4	1.10	346.2	1.14	0.96 (0.84, 1.10)	306.8	1.53	298.3	1.58	0.97 (0.85, 1.10)	573.4	0.042	570.7	0.068	0.61 (0.37, 1.02)

Note. RR = rate ratio; CI = confidence interval.
[a]Six or more liquid or semiliquid bowel motions on the worst day.
[b]Per 1000 child-years; only the first occurrence of each event within the study was included (see text).
[c]χ^2 (trend) = 1.97, P = .16.
[d]χ^2 (trend) = 0.56, P = .45.
[e]χ^2 (trend) = 0.22, P = .64.

TABLE 4—The Impact of Vitamin A Supplementation on Child Mortality according to Number of Doses Received

No. Doses Received	Total Doses[a]		Sequential Doses[b]	
	Rate Ratio[c]	95% CI	Rate Ratio[c]	95% CI
1	0.99	0.78, 1.26	0.99	0.78, 1.25
2	0.54	0.39, 0.73	0.53	0.38, 0.72
3	0.77	0.51, 1.16	0.79	0.52, 1.20
4	0.87	0.53, 1.44	0.91	0.54, 1.55
5	0.74	0.42, 1.30	0.79	0.44, 1.41
6	0.73	0.37, 1.44	0.73	0.37, 1.44
1–6	0.81	0.68, 0.98	0.82	0.68, 0.98*

[a] χ^2 (trend) = 0.75, P = .39.
[b] χ^2 (trend) = 1.03, P = .31.
[c] Mean of the mortality rates in the vitamin A clusters divided by mean of the mortality rates in the placebo clusters.
*P = .03.

Impact of Vitamin A Supplementation

Time since dose was received. The exact date of death was established for 748 (83.9%) of the deaths that occurred among trial children in the Survival Study, 335 (84.4%) in the vitamin A clusters and 413 (83.4%) in the placebo clusters (χ^2 = 0.15, P = .70). The mortality rates in each of the 30-day periods subsequent to a dose are shown by treatment group in Table 2. Although the rate ratio varied from one 30-day period to another, there was no evidence of a trend (χ^2 [trend] = 0.019, P = .89). This was confirmed by testing the treatment–time interaction in the proportional hazards model (χ^2 = 0.023, P = .88).

The rates of first episodes of diarrhea with six or more liquid or semiliquid motions per day, first clinic attendances, and first hospitalizations are shown by treatment group and time since dosing in Table 3. As was the case for mortality, there was no clear evidence of a trend in the rate ratio by time since dosing for any of the three outcomes, and this was confirmed by testing the treatment–time interaction in the proportional hazards model (severe diarrhea, P = .156; clinic attendances, P = .054; hospital admissions, P = .625). Although the P value was close to .05 for clinic attendances, this was largely related to a low rate ratio in the first month after dosing (Table 3). The apparent decline in morbidity rates in both treatment groups over the five time intervals, which was most evident for the commoner outcomes, was an artifact resulting from only the first event in each round being included in the analysis for each child. This meant that "high-risk" children were rapidly lost to follow-up because they had already experienced their first event, leaving only lower risk children under observation.

Number of doses received. Mortality rate ratios (vitamin A:placebo) within the Survival Study were calculated for all children who had ever received a dose of either vitamin A or placebo according to the total number of doses received during the trial (Table 4). There was no evidence of a trend (χ^2 [trend] = 0.95, P = .33). Similar results were obtained when the analysis was restricted to children who had never missed a dose they were eligible to receive (χ^2 [trend] = 0.70, P = .40) and when the analysis was based on the maximum number of sequential doses that a child had received during the trial (χ^2 [trend] = 0.72, P = .40; see Table 4).

Within the Health Study, although the rate ratios of severe diarrhea and clinic attendances increased from less than 1.0 to more than 1.0 as the total number of doses received increased from one to three, there was no statistically significant trend in any of the three morbidity outcomes (Table 5). Since, in the Health Study, the maximum number of doses a child could receive was three, and most children received all three doses, there was virtually no difference between the results of the analysis based on the total number of doses received by a child and the results of the analysis based on the maximum number of sequential doses received (data not shown).

Time of year in which supplement was given. The rate ratios of the impact of vitamin A supplementation on mortality were 0.74 (95% CI = 0.55, 1.01) when the dose was given during the late dry season (February/March), 0.71 (95% CI = 0.53, 0.93) during the early wet season (June/July), and 0.96 (95% CI = 0.72, 1.27) during the early dry season (October/November). There was no significant difference between these three results (χ^2 [heterogeneity] = 3.64, 2 *df*, P = .16).

Discussion

In the Ghana Vitamin A Supplementation Trials, the impact of supplementation on child morbidity was limited to a reduction in the incidence of severe illness and was most pronounced for severe diarrhea and for illnesses severe enough to provoke a clinic attendance or hospital admission.[1,7] It is for this reason that the analyses reported here have concentrated on episodes of severe diarrhea, clinic attendances, hospital admissions, and mortality.

We found no evidence of a decline in the protection afforded by prophylactic, large doses of vitamin A against mortality and severe morbidity over a 120- to 150-day (4- to 5-month) follow-up period between doses. Nor does there appear to have been any cumulative protection against mortality or severe morbidity according to the number of doses the child had previously received at intervals of approximately 4 months, and the degree of protection did not vary significantly according to the time of year (study round) in which the supplement was given.

It would appear that, at least in this population, an interval of at least 4 months between high doses of vitamin A may be adequate for the prevention of both severe morbidity and mortality. On the other hand, there was no cumulative increase in the impact according to the number of doses the child had received previously.

It is not possible to be certain that these findings would also occur in other populations deficient in vitamin A. The xerophthalmia prevalences among children at the start of the trials were 0.7% (Survival Study) and 1.5% (Health Study).[1] The proportions of children with low baseline serum retinol levels were substantial in both trial populations. In a subsample of the Survival Study children, 14.4% were severely deficient (<0.35 μmol/L) and 42.5% were moderately deficient (0.35 to 0.69 μmol/L); the equivalent proportions of the Health Study children were 15.8% and 57.6%.[1] More frequent doses (e.g., at intervals of 3 months) might be appropriate in populations with higher prevalences of xeroph-

thalmia and severe biochemical deficiency.

This study did not provide evidence to support restricting dosing to certain times of year. The impact of vitamin A supplementation appeared to have varied for different causes of death within this trial population; the most substantial effects involved acute gastroenteritis–related deaths, but there was no apparent effect on deaths related to either malaria or acute respiratory infection.[1] These three causes accounted for almost two thirds of the deaths to which a cause could be allocated.[1] The fact that there was no clear difference in impact according to the time of year in which the supplement was given may well have been a result of the peak incidence of deaths from all three of these causes overlapping in the second half of the calendar year (data not shown).

Overall, the results imply that, at least within this population of children, an interval of 4 months between high-dose vitamin A supplements is likely to be adequate, and there was no clear evidence that supplements would be more effective if given at certain times of year. These results have important implications for the planning of population-wide child vitamin A supplementation programs both in northern Ghana and in areas of West Africa and elsewhere that have similar levels of vitamin A deficiency and similar morbidity and mortality profiles. □

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