Is 12-monthly vitamin A supplementation of preschool children effective? An observational study of mortality rates for severe dehydrating diarrhoea in Yemen

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Background. Two nation-wide vitamin A supplementation campaigns were launched in the Republic of Yemen. The first (November 1997) targeted children aged 12 - 59 months, and the second (November 1998) targeted the 12 - 59 and the 6 - 11-month age groups.

Objective. To document the impact of the two annual vitamin A supplementation campaigns on mortality from severe dehydrating diarrhoea.

Design. Observational study.

Setting. Four major hospitals in Sana'a, Yemen.

Results. The total under-5-year case fatality rate (CFR) was 11% in the pre-dosing year and 8.4% in the first post-dosing year. The reduction was marginally significant (odds ratio (OR) 0.75, 95% confidence interval (CI): 0.56 - 0.99), since only one age group was targeted. CFR in the second year was further reduced to 7.6% (OR 0.67, CI: 0.48 - 0.86), since two age groups were targeted.

Among the older than 12-month age groups, the first and second post-dosing year CFRs were 4.6% and 5.7%, significantly lower than 11.9% in the pre-dosing year (OR 0.36, CI: 0.25 - 0.5, and OR 0.45, CI: 0.32 - 0.63), respectively. The first 6-month CFR showed a clinically significant reduction, but this was not statistically significant (OR 0.48, CI: 0.16 - 1.35, and OR 0.54, CI: 0.18 - 1.54). Reduction in the last 6 months was statistically significant (OR 0.2, CI: 0.04 - 0.72 and OR 0.38, CI: 0.14 - 0.96), respectively.

Among the 6 - 12-month age groups, the first post-dosing year CFR was 8.7%, and 10.1% in the pre-dosing year, a statistically non-significant reduction (OR 0.84, CI: 0.54 - 1.31), since these children were not supplemented in the first campaign. The campaign's first and last 6 months also showed a non-significant reduction (OR 0.98, CI: 0.51 - 1.91, and OR 0.73, CI: 0.39 - 1.36) respectively. When targeted in the second campaign, CFR was significantly reduced to 4.9% (OR 0.46, CI: 0.32 - 0.66), and 6-month subgroups showed a similar significant trend (OR 0.41, CI: 0.17 - 0.94, and OR 0.49, CI: 0.25 - 0.94), respectively.

The under-6-month CFR in the 3-year study period was unchanged (11.4%, 10.1% and 12%).

Conclusion. A significant reduction in CFR among children aged 6 - 59 months hospitalised with severe dehydrating diarrhoea was observed following two annual vitamin A supplementations targeting this age group in Yemen.

In 1995, clinical vitamin A deficiency was reported to be a major health problem in 38 countries in the world, including the Republic of Yemen.[1]

Vitamin A deficiency has been shown to increase the risk of common childhood infections,[2,3] and recent data indicate that childhood mortality increases with mild vitamin A deficiency,[4] while vitamin A supplementation has been shown to reduce morbidity and mortality.[5] Improvement in vitamin A status has been reported to reduce the risk of death from childhood infections by as much as 34 - 54%.[6-8]

Diarrhoea is the leading cause of morbidity and mortality among young children in Yemen. It has been reported as the single largest health threat to Yemeni children and the most common specific symptom before death. In a recent community survey, 28% of children aged under 5 years had diarrhoea and 7% had bloody diarrhoea in the 2 weeks preceding the survey. Among the 6 - 11-month and 12 - 23-month age groups, diarrhoea and bloody diarrhoea were reported at 39% and 6.3%, and 38% and 9% respectively. In this survey diarrhoea was also reported to be the probable cause of death in 58% of the 1 - 11-month age group and 56% of the 12 - 59-month age group in the preceding 5-year period.[9] In this regard, it should be borne in mind that knowledge and use of oral rehydration therapy (ORT) remains very low in Yemen. It has been reported that more than 70% of mothers do not use any oral rehydration solution when their children develop diarrhoea.[10]

Since there have been few attempts to determine the impact of large-scale vitamin A supplementation on survival of hospitalised children in Yemen, the objective of this observational opportunistic study was to document the effect of 12-monthly vitamin A supplementation on the case fatality for children aged under 5 years hospitalised with severe dehydrating diarrhoea.

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Patients and methods

Between 23 and 25 November 1997, during a nationwide oral polio vaccination campaign, children aged 12 - 59 months were targeted to receive vitamin supplementation. Each child was given a single oral dose of 200 000 IU vitamin A by a nurse (vitamin A (retinol), RP Scherer SPA, Aprilia, Italy). During the campaign 516 863 children in the targeted age group in the catchment areas of Sana'a city and Sana'a province (both with a total population of 2 million) were supplemented covering approximately 97% of the target population of 532 586 children. In November 1998 a second supplementation programme was launched targeting the same age group, using the same dose, and covering approximately 93% of children in this age group (567 610 of 613 880) in these areas. During the second campaign the 6 - 11-month age group was also supplemented; each infant was given 100 000 IU of oral vitamin A by a nurse, with 100% coverage of this age group in the catchment areas (Ministry of Health, Yemen 1998/99 data). The coverage rate of vitamin A supplementation for children aged 6 - 59 months in all the regions of Yemen in 1998 - 1999 was reported to be 100%.[11] Both campaigns were funded by UNICEF-Yemen. Yemen has a total population of 16 million of whom 19% are aged under 5 years.

Location of the study

This study was conducted in four major government hospitals in Sana'a, Yemen, with a total of 160 paediatric beds and more than 100% occupancy, serving Sana'a city and Sana'a province, both with approximately 2 million inhabitants. All four hospitals have walk-in paediatric outpatient and emergency units. The hospitals follow the World Health Organisation (WHO) guidelines for hospital management of severe dehydrating diarrhoea,[12] and several workshops have been conducted for the hospital staff on these guidelines. Because of severe bed shortages and limited resources, the policy of these hospitals is to admit only severely dehydrated children. Those with milder symptoms are treated in the emergency units according to the WHO guidelines.[12] Most of the patients in the catchment areas use these facilities as their first contact point, and usually arrive at the emergency units severely dehydrated.

Pre-dosing data collection

All children under 5 years of age admitted to the paediatric wards of the four hospitals between 1 December 1996 and the end of November 1997, with vomiting and diarrhoea and signs of severe dehydration as defined by the WHO guidelines,[12] were included in the study. Information from each child's case notes was recorded to ascertain the date of admission, age, sex, diagnosis and outcome, whether alive or dead on discharge. All the information was recorded on special data collection sheets each month. Patients included in the study who died during the 12-month study period, the first 6 months, and the last 6 months, were grouped in the under-6-month, 6-12-month, and above-12-month age groups.

Post-dosing data collection

All children of the same age groups admitted to the same hospitals with vomiting and diarrhoea and signs of severe dehydrating diarrhoea as defined by the WHO guidelines,[12] were included in the study. Information on the date of admission, age, sex, diagnosis and outcome on discharge, was recorded during the first post-dosing year (December 1997 - November 1998), and the second post-dosing year (December 1998 - November 1999), on a monthly basis. Patients included in the study and those who had died during the year, and its 6-month periods, were grouped in age groups as in the pre-dosing year. To avoid selection bias only severely dehydrated children were included in this study, and in all the four hospitals the treating physicians were unaware of the nature of the study.

Statistical analysis

The data were analysed using the Epi-Info software package (Version 6). Chi-square test for trend with *p*-value and odds ratio (OR) with 95% confidence intervals (CI) and exact confidence limits, were used to compare variables of the pre- and post-dosing study groups and were determined according to the extended Mantel-Haenezel test.

Results

The study populations admitted with severe dehydrating diarrhoea during the pre-dosing and the 2 post-dosing years as well as their first and last 6-month study periods were comparable in terms of male/female ratio and age group distribution. The total admissions in the first and second post-dosing years were increased by 7% and 13.6% respectively compared with the pre-dosing year, but the age group proportions were comparable (Table I).

Compared with the pre-dosing year, the overall total case fatality rate (CFR) in the first post-dosing year, in which one age group was targeted, was lower by over 23%. When two age groups (6 - 11 months and 12 - 59 months) were supplemented in the second year, a statistically significant reduction of more than 30% was observed (Table II).

Age-specific CFR was lower by 61% in the over-12-month age group in the first post-dosing year, and by 52% in the second post-dosing year, both statistically significant (Table II).

The 6 - 12-month age group CFR was lower by a non-significant 14% in the first post-dosing year, since this age group was not targeted in the first vitamin A campaign, while a significant reduction of 51% in CFR was evident in the second year when they were supplemented. No change in CFR in the

Table I. Severe dehydrating diarrhoea. Baseline characteristics: pre- and post-dosing years and their first and last 6-month subgroups (*N* (%))

Period	Males	Under 6 months	6 - 12 months	Above 12 months
Pre-dosing year	662	458	474	243
N = 1 175	(56)	(39)	(40)	(21)
First post-dosing year	697	466	553	238
N = 1 257	(55)	(37)	(44)	(19)
Second post-dosing year	680	472	583	280
N = 1 335	(51)	(35)	(44)	(21)
First 6-month subgroups				
Pre-dosing year	311	184	205	88
N = 477	(65)	(39)	(43)	(18)
First post-dosing year	366	218	248	114
N = 580	(63)	(37)	(43)	(20)
Second post-dosing year	298	183	223	101
N = 507	(59)	(36)	(44)	(20)
Last 6-month subgroups				
Pre-dosing year	351	274	269	155
N = 698	(50)	(39)	(39)	(22)
First post-dosing year	331	248	305	124
N = 677	(49)	(37)	(45)	(18)
Second post-dosing year	382	289	360	179
N = 828	(46)	(35)	(43)	(22)

Table II. Severe dehydrating diarrhoea — pre- and post-dosing year age-specific case fatality (CFR) (*N* (%))

Age group	Pre-dosing year CFR	First post-dosing year CFR	Second post-dosing year CFR
Under 6 months*			
N	52/458	47/466	57/472
%	11.4	10.1	12
OR	1	0.9	1.1
95% CI		0.56 - 1.36	0.7 - 1.63
6 - 12 months†			
N	48/474	48/553	29/583
%	10.1	8.7	4.9
OR	1	0.84	0.46
95% CI		0.54 - 1.31	0.28 - 0.77
Above 12 months‡			
N	29/243	11/238	16/280
%	11.9	4.6	5.7
OR	1	0.36	0.45
95% CI		0.16 - 0.76	0.22 - 0.88
Total §			
N	129/1 175	106/1 257	102/1 335
%	11	8.4	7.6
OR	1	0.75	0.67
95% CI		0.56 - 0.99	0.51 - 0.86

* X^2 for trend 0.13, $p = 0.72$.
† X^2 for trend 10, $p = 0.0015$.
‡ X^2 for trend 7, $p = 0.008$.
§ X^2 for trend 8.4, $p = 0.004$.

under-6-month age group was noted during the 3-year study period (Table II).

A statistically significant reduction of 56% and 48% in CFR was observed in the 6 - 12-month age group during the first and last 6 months of the second post-dosing year respectively. No statistically significant reduction was observed during the same 6-month periods of the first post-dosing year, since this age group was not targeted in the first campaign (Table III). A non-significant CFR reduction (25%) was observed in the last 6-month CFR for this age group (Table III), which may be due to the influence of patients aged 12 months who were supplemented with vitamin A, but included in this age group according to the study protocol.

In the above-12-month age group, a clinically significant reduction of 48% and 41% in CFR was observed during the first 6 months of the first and second post-dosing years respectively, although statistical analysis showed a non-significant reduction trend (X^2 for trend 1.7, OR 0.48, 95% CI: 0.16 - 1.35, and OR 0.54, CI: 0.18 - 1.54). This may be due to the small number of patients in this subgroup. The last 6 months of the two post-dosing years showed a significant reduction of 78% and 59% in CFR respectively (Table III).

Discussion

The pre-dosing overall CFR for children admitted with severe dehydrating diarrhoea found in this study was similar to the rate previously reported in Yemen.[13] It is worth noting that the all-cause age-specific mortality rate in the 12 - 59-month age group in Sana'a city and Sana'a province were 9.3% and 11% and in the under 12-month age-group, 7.8% and 8.9% respectively.[15]

Our study documented a clinically significant reduction in CFR for severe dehydrating diarrhoea in the older than 12-month age groups during the 2 post-dosing years, and in the 6 - 12-month age group during the second post-dosing year compared with the pre-dosing year, which may be associated with the vitamin A supplementation in the childhood community (Table II).

Selection bias was avoided by including only severely dehydrated children. Less severe cases are usually treated in the emergency and outpatient units because of severe bed shortages and limited resources. The treating physicians were also unaware of the nature of the study. Parents of Yemeni children tend to seek medical care for diarrhoea late in the course of the illness, when the children are severely dehydrated

Table III. Severe dehydrating diarrhoea — first and last 6-month subgroups, age-specific case fatality (CFR) (*N* (%))

Age group	Pre-dosing year CFR	First post-dosing year CFR	Second post-dosing year CFR
6 - 12 months			
First 6 months*			
N	21/205	25/248	10/223
%	10.2	10	4.5
OR	1	0.98	0.41
95% CI		0.51 - 1.91	0.17 - 0.94
Last 6 months†			
N	27/269	23/305	19/367
%	10	7.5	5.2
OR	1	0.73	0.49
95% CI		0.39 - 1.36	0.25 - 0.94
Above 12 months			
First 6 months‡			
N	12/88	8/114	8/101
%	13.6	7	7.9
OR	1	0.48	0.54
95% CI		0.16 - 1.35	0.18 - 1.54
Last 6 months§			
N	17/155	3/124	8/179
%	11	2.4	4.5
OR	1	0.2	0.38
95% CI		0.04 - 0.72	0.14 - 0.96

* X^2 for trend 4.8, $p = 0.03$.
† X^2 for trend 5.4, $p = 0.02$.
‡ X^2 for trend 1.7, $p = 0.2$.
§ X^2 for trend 5.7, $p = 0.017$.

and unable to drink, resulting in a high percentage of hospital beds occupied by children suffering from diarrhoea. In many cases the children arrive too late to be saved, which may explain the reports that 40% of in-hospital diarrhoeal deaths occur within the first 24 hours of admission.[10]

Survival bias was unlikely in this study since case management of severe dehydrating diarrhoea in the four hospitals remained unchanged and complied with the WHO guidelines during the 3-year study period. Hospital conditions and treatment facilities that may influence survival remained unchanged, which may explain the unchanged CFR in the under-6-month age groups over the 3-year study period. It is worth noting that the percentage of central government expenditure allocated to health remained unchanged at 4% over the 3-year study period[11] compared with 10% in 1992.[14]

It is unlikely that the reduced CFR in the post-dosing years was due to improvement in the nutritional and health status of children in the catchment areas. In Sana'a city where this study was conducted, access to safe water supply remains very limited with only one-third of water to households coming from public supply and much of the remainder coming from shallow wells with contaminated ground water beneath Sana'a city. Nutritional status of the childhood community in Yemen has changed little over the last two decades and malnutrition of children under 5 years in Yemen is among the highest in the world. The health care system in Yemen has reached a point of crisis with low coverage, poor quality and poor utilisation and is unable to meet the special needs of the Yemeni children. In addition, government funding for childhood nutritional activities virtually non-existent.[10] This, together with poor sanitation and an unsafe water supply make the risk of enteric infections and malnutrition worse in the post-dosing years.

In Yemen sanitation facilities and improved drinking water supply have not changed, and may have worsened in the post-dosing years. In 1997, 77% of the population was using safe drinking water, and 66% had adequate toilet facilities[9] compared with 69% and 45% respectively in 1999.[11] This may in part explain the increased number of children hospitalised with severe dehydrating diarrhoea in the 2 post-dosing years (Table I).

The use of ORT remains very low in Yemen and has not increased significantly to influence diarrhoea-related mortality in the 2 post-dosing years. In the 1992 survey,[15] only 27% of diarrhoea cases were treated with ORT compared with 32% in the 1997 survey,[9] while the UNICEF statistical tables for 1999 reported 35% oral rehydration solution usage rate in Yemen.[11] The ability of the health care system to respond to childhood diarrhoea in Yemen is reported to be very limited. A previous report stated that only 1.5 million packets of oral rehydration solution were distributed to health facilities throughout Yemen, in essence one packet for every two children per year, far too little to treat the reported 5 - 9 diarrhoeal episodes per year in Yemeni children.[10]

The reduction in case fatalities in this study was also unlikely to have been influenced by parallel interventions such as improved vaccination coverage and/or change in breast-feeding practices, since both did not change in the 3-year study period. Although immunisation coverage in Yemen varies from region to region, the 1997 survey[9] reported that among children aged 12 - 23 months who received their immunisation during the pre-dosing year (December 1996 - November 1997), only 14% had no vaccinations. Recent UNICEF statistical tables[11] indicate that the percentage of Yemeni children who were immunised between 1997 and 1999 were 72%, 72% and 74% for DPT, oral polio, and measles respectively. In Sana'a city and Sana'a province where this study was conducted, the immunisation coverage rates for these vaccines were 88%, 88% and 75% in 1996; 76%, 76% and 70% in 1997; 80%, 80% and 75% in 1998; and 75%, 75% and 80% in 1999 respectively.[10] Breast-feeding rate and duration in the 2 post-dosing years were comparable to those in the pre-dosing year: 25% of infants aged under 3 months were exclusively breast-fed, 79% of the 6 - 9-month age group were breast-fed and received complementary foods, and 41% were still breast-feeding at 23 months of age.[9,11]

Potential confounders such as improved hospital facilities, improved nutritional status of Yemeni children, better sanitation, and safe water supply could not have improved survival significantly in the older than 12-month age groups in the 2 post-dosing years or in the 6 - 12-month age group in the second post-dosing year, since such confounders should also have reduced CFR among those younger than 6 months of age who were not targeted in the two vitamin A supplementation campaigns, and those in the 6 - 12-month age group who were not supplemented in the first campaign (Table II).

Although diarrhoea-related mortality has been declining worldwide[16] and more than 50% reduction in diarrhoea mortality in a 3-year study period has been reported in Brazil without vitamin A supplementation,[17] the situation in Yemen is probably different. The Brazilian study[17] reported that ORT and breast-feeding doubled in that country. In the poorest areas of the Brazilian study site 98% of the houses had water, which is much better than in the best areas of Sana'a, and in Yemen where only 69% of the population has access to safe drinking water. The prevalence of mild to severe malnutrition was reported to be 5.5% for weight/age and 8.7% for height/age in the Brazilian study areas, compared with 46% and 52% respectively in Yemen.[10] Nutritional data specific for Sana'a population are lacking; however, the absolute number of poor people is reported to be higher in Sana'a than in other provinces in Yemen.[10] A recent survey indicates that poverty in Yemen has almost doubled between 1992 and 1998, with

households living in poverty rising from 19% in 1992 to 33% in 1998.[18] It is worth noting that the prevalence of malnutrition among Yemen children was the highest in 1999 where moderate to severe underweight and moderate to severe stunting were reported to be 61% and 52%,[11] compared with 34% and 49% respectively in 1992.[14] Other factors that may reduce diarrhoea mortality such as decreased percentage of low-birth-weight infants, improved sanitation facilities, and increased use of ORT, are also far better in Brazil than in Yemen.[11] It is therefore possible that vitamin A supplementation in Yemeni children may have influenced the reduced case fatalities among children hospitalised with severe dehydrating diarrhoea observed in the 2 post-dosing years.

Our results support the hypothesis that the impact of vitamin A supplementation in reducing diarrhoea-related mortality is remarkably evident in children with severe dehydrating diarrhoea. Barreto *et al*.[19] reported that such impact increases with the severity of the diarrhoeal disease, and two meta-analyses have concluded that vitamin A supplementation was associated with significant reduction in diarrhoea-specific mortality.[6,20]

In this study the possible effect of vitamin A supplementation on diarrhoea mortality may have continued beyond 6 months post-dosing in the targeted age groups, since the reduction in CFR during the last 6 months of the post-dosing years is still remarkably significant compared with the last 6 months of the pre-dosing year (Table III). This important finding in our study needs further evaluation in a controlled clinical trial.

Although a recent study[21] reported reduced serum retinol concentrations 4 months post-dosing, the limitations of the available methods to assess vitamin A status in infants have been acknowledged. Previous reports have indicated that serum retinol levels are not accurate indicators of total body reserves.[22,23]

Judging by the clinical outcome of our study, and the clinically significant reduction in CFR observed in the first and the last 6-month periods of the post-dosing years compared with those of the pre-dosing year, a 12-monthly vitamin A supplementation programme is probably an effective strategy in reducing diarrhoea-related mortality. It is possible that tissue retinol levels remain available to modulate the immune system for up to 12 months. Six-monthly dosing may be difficult to implement due to logistic, economic and resource difficulties in countries such as Yemen.

The strength of this study lies in the consistency of the findings among the targeted age groups during the post-dosing years and their 6-month study periods as indicated by the constant trend in the odds ratio with a progressive decrease in the odds of case fatality among those age groups that developed severe dehydrating diarrhoea.

The limitation of this study was the small number of children older than 12 months of age in both pre- and post-dosing populations. This may have led to greater variability in our statistical analysis of the 6-month subgroups and inadequate statistical power to show a possible sustained association between vitamin A and reduced case fatality up to 12 months.

Conclusion

A clinically significant reduction in case fatalities among children aged 6 - 59 months hospitalised with severe dehydrating diarrhoea in Yemen was observed following two 12-monthly vitamin A supplementation campaigns.

The reduction in case fatality was also observed in the first and the last 6-month periods of the 2 post-dosing years.

This study was supported in part by a grant from the Faculty of Postgraduate Studies and Research, Sana'a University (pre-dosing and first post-dosing years), and UNICEF-Sana'a, Yemen (second post-dosing year).

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