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A randomized, double-blind, placebo-controlled clinical trial of vitamin A in Mozambican children hospitalized with non-measles acute lower respiratory tract infections

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Summary

OBJECTIVE The objective of this study was to test the potential of routine vitamin A supplementation at admission to speed up recovery during hospitalization for acute lower respiratory tract infections (ALRI) and to decrease the levels of morbidity at 6 weeks after discharge. The study was conducted in the Central Hospital of Maputo (CHM), Mozambique, from 1995 to 1997.

METHODS Children aged 6–72 months with ALRI admitted to the paediatric wards of the CHM were assigned to a supplementation group ($n = 71$, receiving 200 000 IU of vitamin A) or a control group ($n = 93$, receiving a placebo).

RESULTS The prevalence of vitamin A deficiency was very high and similar between the two groups. The median number of inpatient days for the supplementation group was 3, for the placebo group 4 days. On day 5 the rate of clinical discharge was 88.4% ($n = 61/69$) in the experimental intervention group and 73.9% ($n = 65/88$) in the placebo group ($P = 0.023$).

CONCLUSION We found a statistically significant reduction in duration of admission among vitamin A-supplemented children with ALRI. This effect is in line with what is known about the role of vitamin A in human defence and immune mechanisms and with the serological evidence of the extent of vitamin A deficiency among the children in this trial.

keywords Vitamin A, supplementation, ALRI, RCT, Mocambique

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Introduction

Acute respiratory infections are the leading cause of mortality in children under 5 in developing countries, with about 3.8 million deaths annually (Kirkwood *et al*. 1995). In Mozambique acute lower respiratory infections (ALRI) are responsible for about 19% of inpatient deaths in the Paediatrics Department of the Central Hospital of Maputo (CHM) (Julien *et al*. 1995).

Vitamin A deficiency is clearly associated with increased child morbidity and mortality (Sommer *et al*. 1983, 1984; Milton *et al*. 1987). In Mozambique the limited data available suggest that mild vitamin A deficiency has been common but that severe forms have been extremely rare (Santos 1974; Julien *et al*. 1993).

In community trials, vitamin A supplementation, although reducing overall mortality, has failed to show any significant impact on mortality associated with ALRI (Vitamin A and Pneumonia Working Group 1995). Despite the beneficial effect of vitamin A supplementation in measles-related pneumonia (Hussey & Klein 1990; Coutsoudis *et al*. 1991), the results of clinical trials in nonmeasles-related pneumonia

have been disappointing (Kjolhede *et al.* 1995; Fawzi *et al.* 1996; Kyran *et al.* 1996; Nacul *et al.* 1997).

The theoretical evidence for the possible beneficial effects of vitamin A supplementation in ALRI include:

- a sustained decrease in circulating levels of retinol during ALRI;
- the observation of an increased *in vitro* adherence of bacteria to respiratory epithelial cells in patients with vitamin A deficiency;
- the rapid destruction of epithelial cells in ALRI; poor repair of epithelial surfaces in children with mild vitamin A deficiency;
- an improved immune response to infection after supplementation (Chandra 1988; Rumore 1993; Kjolhede *et al.* 1995).

This randomized, double blind, placebo controlled clinical trial investigated the potential of routine administration of vitamin A at admission for nonmeasles ALRI to speed up recovery during hospitalization and to decrease postdischarge morbidity.

Population and methods

Children aged 6–72 months admitted with ALRI to the paediatric wards of the CHM were, after obtaining informed consent from the accompanying guardian, assigned to either a supplementation (receiving vitamin A) or a control (receiving a placebo) group, and were followed-up 6 weeks after discharge. The study was approved by the ethics committees of the Prince Leopold Institute, Antwerp, Belgium and CHM, Maputo, Mozambique.

The assignment was made according to a predetermined simple random list. Capsules of vitamin A or placebo were put into an envelope labelled with a code number. This number was only available to a team member not involved with the recruitment and treatment of patients. The vitamin A capsules contained 100 000 IU of vitamin A plus 20 IU of vitamin E and the identical-looking capsules of placebo contained only 20 IU of vitamin E.

Diagnostic criteria were: cough, pyrexia > 37.5 °C, respiratory rate > 50/min plus either crepitations not cleared by coughing or bronchial breathing on auscultation. The paediatrician in charge requested 113 chest X-rays (for 68.9% of the trial children). All showed radiological changes compatible with a diagnosis of bronchopneumonia or pneumonia. If we take the presence of X-ray changes as a diagnostic gold standard, then the positive predictive value of the diagnostic criteria being used in the trial is 100%.

Exclusion criteria were: history of measles or measles vaccination in the 4 weeks preceding admission, clinical signs of vitamin A deficiency, signs of kwashiorkor or marasmus and other concomitant severe diseases (i.e. diseases other than ALRI and independently requiring hospital admission –, e.g. dehydrating diarrhoea and severe malaria).

The children were treated with a standardized ward protocol of penicillin i.m. or i.v. or, alternatively, for the most severe disease forms, chloramphenicol, i.m. or orally. They were further supplemented with a single oral dose of 200 000 IU of an oil formulation of vitamin A or placebo immediately after being recruited into the trial (100 000 IU if the child was < 1 years of age). The size of the sample needed was calculated using the formula

$$n = \frac{p_1 \times (100\text{-}p_1) + p_2 \times (100\text{-}p_2) \times f\,(\alpha,\beta)}{(p_2 - p_1)^2}$$

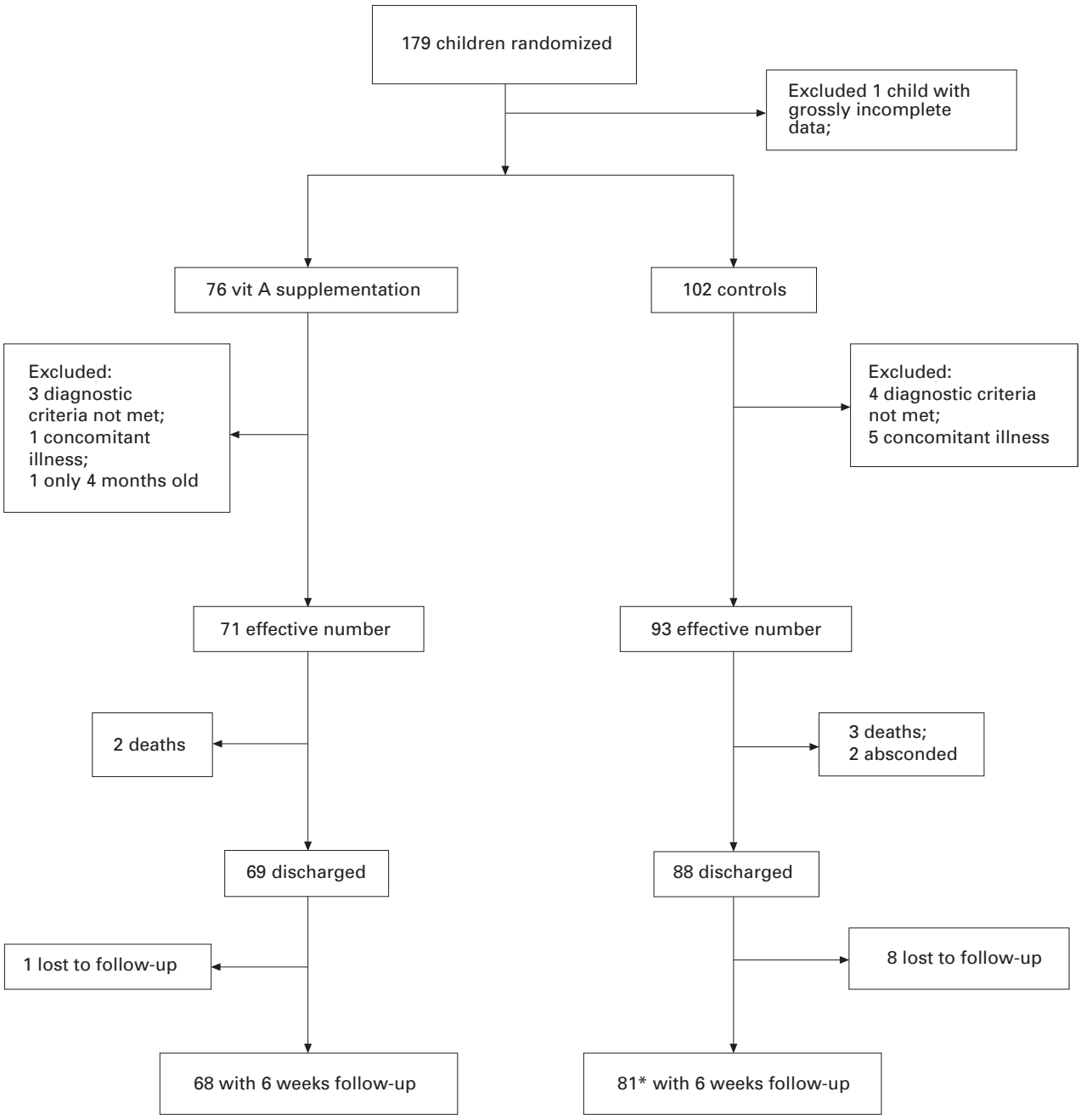
The assumptions to calculate the sample size were that the percentage of children discharged on day five would increase from p_1 (placebo group) $= 65\%$ to p_2 (intervention group) $= 90\%$. If $\alpha = 0.01$ and $\beta = 0.05$ then $f = 17.8$ and n = sample size necessary in each treatment group would be 90 cases and 90 controls. Data were collected using piloted standard schedules. Each schedule included up to 5 components:

- data extracted from hospital-based clinical documents;
- data extracted from home-based health records (road to health card);
- data obtained by interviewing the guardian;
- results of laboratory tests;
- trial identification data.

Routine clinical laboratory analyses were done using the currently in-use methods in the hospital clinical pathology laboratories. On all cases, the serum concentration of retinol (by high-pressure liquid chromatography) (Catigani & Bieri 1983) was determined at the Department of Human Nutrition, University of Stellenbosch, South Africa. Blood samples were stored (in the dark from the time of collection) for a month between − 80° and − 20° C and shipped monthly on dry ice to the reference laboratory. *Plasmodium* microscopy was done for all children, as it is routine in the CHM. Children were X-rayed upon request by the attending clinicians.

After a field pilot in early 1995, the trial was implemented from August 1995 to April 1997 and 179 children were recruited. Of these, 15 were excluded during analysis, 5 in the vitamin A group, 9 in the placebo group. For 1 child the assignment to either placebo or experimental group was unknown and he had grossly incomplete data. Seven children (3 in the vitamin A group and 4 in the placebo group) were excluded, as they did not meet diagnostic criteria. Another 6 (5 in the placebo and 1 in the vitamin A group) had

kwashiorkor or severe malaria; and one child (vitamin A group) was only 4 months old and excluded as a result. The useful sample size was 164. There were 71 in the experimental intervention group and 93 in the placebo group. At 6 weeks postdischarge, the numbers of children were 68 (95.8%) and 81 (87.1%), respectively ($P = 0.056$) (Figure 1).



* one of the two children that absconded from the hospital wards came back to the 6-week follow-up

Figure 1 Trial progress

Table 1 Sociodemographic characteristics of the children recruited into the trial

	Vitamin A supplemented group	Placebo group
Median age (months)	15 ($n = 71$)	13 ($n = 93$)
Male/female	36/35	50/43
Median years of schooling of the mother	5 ($n = 68$)	4 ($n = 93$)
Type of house		
Reed	21 (29.6%)	32 (36.0%)
Zinc	9 (12.7%)	11 (12.4%)
Brick	41 (57.7%)	46 (51.7%)
Median number of divisions in the house*	3 ($n = 69$)	3 ($n = 89$)
Water piped into the house	32/71 (45.1%)	41/93 (44.1%)
Availability of refrigerator	27/68 (39.7%)	33/93 (35.5%)
Median household size	6 ($n = 69$)	6 ($n = 93$)
Median number of children in the household	3 ($n = 70$)	3 ($n = 93$)

* excluding kitchen and bathroom/toilet.

The analysis was by 'intention to treat'. It compared the two groups using either a *t*-test for independent samples (Mann Whitney for nonparametric data) or a (χ^2-test (or, when applicable, the two tail Fisher exact test). The analysis was done with EpiInfo®6.04 (Centers for Disease Control, Atlanta).

Results

There were no relevant or significant differences in sociodemographic characteristics or patterns of breastfeeding between the experimental and placebo groups (Tables 1 and 2). Pre-admission and admission clinical data were also similar (Table 3). Retinol levels were not significantly different in the two trial groups (8.9 + 6.9 μg/dl in the supplemented group and 7.9 + 6.2 μg/dl in the placebo group, $P = 0.450$, Mann Whitney test). This reflects a population with a high prevalence of subclinical deficiency of vitamin A (68.9% and 93.2% had serum retinol levels below 10 μg/dl and 20 μg/dl, respectively).

Table 4 summarizes the most important outcomes of the intervention. The median number of inpatient days for the supplementation ($n = 71$) and the placebo groups ($n = 93$) was 3 and 4 days, respectively. On day 5 the rate of clinical discharge was 88.4% ($n = 61/69$) in the experimental intervention group and 74.2% ($n = 69/93$) in the placebo group (RR 1.9, 95% CI 1.01–3.50, $P = 0.023$). Sixty-nine (97.2%) children from the intervention group and 88 (95.7%) from the placebo group had a clinical discharge; for each group the number of deaths were, respectively, 2 (2.8%) and 3 (3.3%). Only one child in each group was reported as having developed unspecified complications. There were no further differences in the in-hospital duration of fever. For the children that were followed-up 6 weeks postdischarge there were no differences in reported frequency of health care use, reported illness (fever, cough or diarrhoea), or mother's appreciation of the evolution of the child's health postdischarge (Table 4).

If we focus on the 64 children under 12 months of age, the median duration of admission was 3 days in the supplemented group *vs*. 4 days in the placebo group. The rate of discharge on day 5 was 100% (24/24) for the supplemented group and 69.4% (25/36) in the placebo group (RR 1.4, 95% CI 1.2–1.8, $P = 0.002$ two tailed Fisher exact test).

Discussion

This is the first trial to identify a statistically significant reduction in duration of admission among vitamin A supplemented children with ALRI. This effect is in line with what is known about the role of vitamin A in human immune defence mechanisms (Semba 1994), and with the serological evidence of the extent of vitamin A deficiency among the

Table 2 Breast feeding patterns of the children recruited into the trial

	Vitamin A supplemented group	Placebo group
Breastfed before admission	42/70 (60.0%)	57/93 (61.3%)
Exclusively breastfed before admission	5/42 (11.9%)	10/57 (17.5%)
Breastfed 6 weeks after discharge	36/64 (56.3%)	48/78 (61.5%)
Exclusively breastfed 6 weeks after discharge	3/36 (8.3%)	5/48 (10.4%)

Table 3 Pre-admission and admission clinical characteristics of the children recruited into the trial

	Vitamin A supplemented group	Placebo group
Mean duration of the illness before admission*(days ± SD)	3.0 ± 1.7 (n = 66)	2.8 ± 1.6 (n = 88)
Vomiting reported before admission	21/68 (30.9%)	35/93 (37.6%)
Diarrhoea reported before admission	12/71 (16.9%)	18/93 (19.4%)
Cough reported before admission	63/71 (88.7%)	91/93 (97.8%)
Dyspnoea reported before admission	70/71 (98.6%)	88/93 (94.6%)
Loss of appetite/difficulty with feeding before admission	52/68 (76.5%)	64/93(68.8%)
Last meal in hours before admission (± SD)	9.5 ± 6.7 (n = 62)	8.9 ± 7.3 (n = 87)
Fever reported before admission	70/71 (98.6%)	93/93 (100%)
Medication taken before admission	22/68 (32.4%)	40/91 (44.0%)
Traditional medicines taken before admission	21/71 (29.6%)	25/92 (27.2%)
Antibiotics taken before admission	6/67 (9.0%)	15/92 (16.3%)
Road to health card seen	63/70 (90.0%)	88/93 (94.6%)
Mean weight (± SD)	10.2 ± 2.6	10.0 ± 2.6
Indrawing of chest	71 (100%)	93 (100%)
Admission with radiologically confirmed pneumonia	50 (70.4%)	63 (67.7%)
Mean (± SD) serum retinol (μg/dl)	8.9 ± 6.9	7.9 ± 6.2* *

* These exclude children with the problem for more than seven days (4 in the vitamin A group and 5 in placebo group). **P = 0.450, Mann Whitney test.

children recruited into this study. Our results contrast with those of other trials, which have not shown any operational or apparent clinical benefit from the supplementation with vitamin A of children hospitalized with ALRI (Kjolhede *et al*. 1995; Fawzi *et al*. 1996; Kyran *et al*. 1996; Nacul *et al*. 1997).

This difference could possibly be due to the extent of vitamin A deficiency among the children in the CHM, while in the Brazil and Guatemala trials (Kjolhede *et al*. 1995; Nacul *et al*. 1997) the prevalence of subclinical vitamin A deficiency was low. Discharge around the 3rd day of hospitalization, coincident with the clinical improvement in vitamin A group described by Nacul *et al*. (1997), may also have contributed to our findings. In the CHM's overcrowded wards any noticeable clinical improvement would be a justification for earlier discharge. Longer hospitalization, to a point of fuller recovery, might be necessary for a correct assessment of the effect of vitamin A supplementation.

The lack of other effects on the postdischarge evolution is not necessarily due to the low power of the study. It could be due to the study design, the absence of a therapeutic potential for vitamin A or to the way it was administered, namely the dose and the formulation of vitamin A used for supplementation.

A dose of 100 000–200 000 IU of vitamin A as used in the

Table 4 Main impact outcomes of the intervention

	Vitamin A supplemented group	Placebo group
Median days of hospitalization	3 (n = 69)	4 (n = 88)
Clinical discharge on day five		
All children*	61/69 (88.4%)	65/88 (73.9%)
Children less than 12 months**	24/24 (100%)	25/36 (69.4%)
At six weeks follow-up§	n = 68	n = 81
Number of attendance	16/68 (23.5%)	25/80 (31.3%)
Children with ARI in the last two weeks	8/68 (11.8%)	5/73 (6.4%)
Children with fever in the last two weeks	12/68 (17.6%)	9/78 (11.5%)
Children with other illness in the last two weeks	4/67 (6.0%)	0
Children with any illness in the last two weeks	15/68 (22.1%)	15/80 (18.8%)
Children worse than on discharge	1/68 (1.5%)	5/80 (6.25%)

*P = 0.023; **P = 0.002; §each child may report more than one disease; the differences between the two groups are not statisticaly significant (chi square test).

Guatemala study (Kjolhede *et al*. 1995) did not result in a detectable increase of serum vitamin A during the convalescence phase. However, a dose of 200 000–400 000 IU in the Brazil study resulted in sustained increase of the serum retinol levels right into the convalescence period (Nacul *et al*. 1997). The measles trials reporting the use of 200 000 IU of vitamin A did not show any impact in mortality or recovery from measles-associated pneumonia (Ogaro *et al*. 1993; Rosales *et al*. 1996) in contrast to the studies reporting the use of 400 000 IU (Hussey & Klein 1990; Coutsoudis *et al*. 1991). It is our recommendation that future trials in Maputo should compare the use of 200 000 IU with 400 000 IU.

Lastly, the formulation of vitamin A might make a difference. The studies showing the highest impact of vitamin A supplementation are those reporting the use of water-soluble formulations (Hussey & Klein 1990; Coutsodis *et al*. 1991) rather than oil-based preparations (Kjolhede *et al*. 1995; Fawzi *et al*. 1996; Nacul *et al*. 1997) as used also in our trial. These should also be considered in the design of future trials.

In conclusion, this trial provides operational evidence for a beneficial effect of vitamin A supplementation. Were the observed reduction in duration of admission not to be attributed to chance or some confounding factors, it would represent a significant operational advance for the management of severe ALRI in countries with busy overcrowded paediatric wards. On the basis of this trial we recommend that, in Mozambique, children with ALRI should be routinely supplemented with vitamin A. Regarding future trials, it would be useful to compare different formulations of different doses, administered according to different schedules in order to identify the best schedule/formulation for administration of vitamin A.

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