

## Randomised study of effect of different doses of vitamin A on childhood morbidity and mortality

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### Abstract

**Objectives** To determine whether the dose of vitamin A currently recommended by the World Health Organization or half this dose gives better protection against childhood morbidity and mortality.

**Design** Randomised study.

**Setting** A combined oral polio vaccine and vitamin A supplementation campaign in Guinea-Bissau, Africa.

**Participants** 4983 children aged 6 months to 5 years.

**Interventions** One of two doses of vitamin A (recommended and half); oral polio vaccine.

**Main outcome measures** Mortality and morbidity at six and nine months.

**Results** Mortality was lower in the children who took half the recommended dose of vitamin A compared with the full dose at both six months (mortality rate ratio 0.69, 95% confidence interval 0.36 to 1.35) and nine months (0.62, 0.36 to 1.06) of follow-up. There was a significant interaction between sex and dose, the lower dose being associated with significantly reduced mortality in girls (0.19, 0.06 to 0.66) but not in boys (1.98, 0.74 to 5.29). The lower dose of vitamin A was consistently associated with lower hospital case fatality in girls (0.19, 0.02 to 1.45). Paradoxically, in children aged 6-18 months, the low dose was associated with slightly higher morbidity.

**Conclusions** Half the dose of vitamin A currently recommended by WHO may provide equally good or better protection against mortality but not against morbidity.

### Introduction

Studies have shown that vitamin A supplementation given to children aged over 6 months reduces all cause mortality by 23%<sup>1</sup> to 30%<sup>2,3</sup> in low income countries. The World Health Organization recommends that supplements should be given when children are vaccinated. Current recommended doses are 100 000 IU at age 6-11 months and 200 000 IU at age  $\geq$  12 months, every 3-6 months. The effect of supplementation may not be due exclusively to the prevention of vitamin A deficiency.<sup>4</sup> For instance, there is no clear evidence that a large dose is better than a small dose.<sup>5,6</sup>

In Guinea-Bissau, a combined polio vaccine and vitamin A campaign took place in November 2002.

Given the uncertainty about the best dose of vitamin A,<sup>4</sup> we examined whether the dose currently recommended by WHO or half this dose gives a better protection against childhood morbidity and mortality.

### Methods

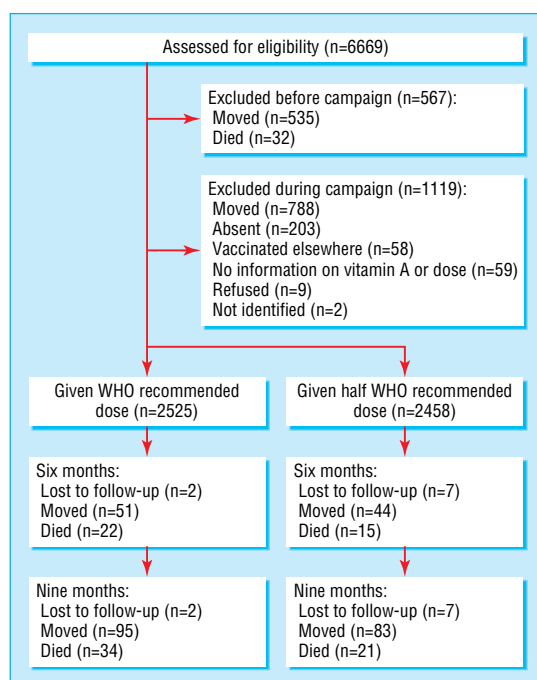
The Bandim Health Project has a demographic surveillance system in several districts of Bissau, the capital of Guinea-Bissau. All children aged  $<$  3 years are visited every third month to obtain information on vaccinations, arm circumference, admission to hospital, and survival. Information on vaccinations is also collected at the two local health centres, where all vaccinations are monitored. Furthermore, the project registers all admissions to the only paediatric ward in the country. The national polio immunisation days were organised as two house to house campaigns lasting for one week each in October and November 2002.

**Protocol**—During the campaign in November, vitamin A supplementation was also offered to all children aged 6 months to 5 years. Apart from such national immunisations days, there is no routine vitamin A supplementation in Guinea-Bissau. We examined the effects of doses of vitamin A on mortality, admission to hospital, mid-upper arm circumference, and diarrhoea, the hypothesis being that a lower dose would offer better protection against morbidity and mortality. We enrolled all eligible children. From a power calculation, we estimated we needed to enrol 5400 children (see bmj.com). The study was explorative as we did not expect to be able to document a significant reduction in mortality.

**Assignment**—Children were randomised to receive vitamin A orally in doses of either 50 000 IU or 100 000 IU to infants aged 6-11 months and 100 000 IU or 200 000 IU to children aged 12-59 months (see bmj.com). Slightly more children received the full dose of vitamin A, possibly because assistants classified a few children who received the full dose elsewhere as having received it in the present study.



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Process through phases of trial

**Masking**—Both assistants and mothers were aware which dose of vitamin A the child received, but those assistants assessing outcome were unaware of the hypotheses being studied.

**Participant flow and follow-up**—The figure shows the flow of children through the study. The large number of children excluded because they had died or moved before the campaign were mainly in the 3-4 year age group who had not had regular surveillance visits since they became 3 years old. We measured the effect of dose for various health indicators, including mortality, admissions to hospital, and mid-upper arm circumference. We carried out a simple verbal autopsy for all children who died, allowing us to distinguish between deaths probably caused by infectious diseases and injuries. Though we planned the study to last six months, the period in which vitamin A is assumed to have an effect, we extended it by three months because of a surprising sex interaction observed after six months. For children less than 18 months old at the time of supplementation project assistants visited their homes every month to collect health information. Similar numbers of children were missing in the two groups.

**Statistical analysis**—We analysed data on survival using Cox proportional hazard models with age as the underlying time. Similarly we analysed data on admission to hospital after vitamin A supplementation with age as the underlying time and robust standard errors to adjust for repeated admissions. We also assessed differences in hospital case fatality. As we had the morbidity data (yes/no) in one month intervals, we analysed these data using discrete time survival models.

## Results

At baseline, there were slightly more infants aged 6-11 months in the group that received the smaller dose (16% *v* 12%). Otherwise, the two randomisation groups were comparable (see [bmj.com](http://bmj.com)). Age group was the only risk factor that changed the estimates by more than 5% and was controlled for in all subsequent analyses.

Mortality at six and nine months after supplementation was lower, though not significantly so, for children who had received the half dose (table). Post hoc subgroup analyses showed a highly significant inversion of the effect ( $P = 0.004$  for homogeneity). While the lower dose was clearly better for girls the full dose might have been slightly better for boys (table). At nine months, the pattern remained the same, with a significant inversion in the effect of dose for boys and girls ( $P = 0.02$  for homogeneity). There was no difference in the effect of dose during the three periods of three months of follow-up. Additional post hoc subgroup analyses of this finding showed that the differential effect was most pronounced among the children aged > 18 months at the time of supplementation, the mortality rate ratios of the half versus the recommended dose being 1.04 (0.32 to 3.41) and 0.74 (0.20 to 2.77) in boys and girls aged 6-17 months, but 1.23 (0.48 to 3.19) and 0.13 (0.03 to 0.58) in those aged 18-60 months.

The beneficial effect of a half dose compared with a full dose was also apparent among children admitted to hospital (see [bmj.com](http://bmj.com)). Slightly fewer children who received the half dose were admitted during the nine months of follow-up and the hospital case fatality tended to be lower for girls who had received the low dose (0.19, 0.02 to 1.45) but not for boys (1.60, 0.48 to 5.30). The case fatality tended to differ by dose for girls and boys ( $P = 0.07$  for homogeneity).

In the subgroup of 1337 children aged < 18 months at the time of supplementation, receiving half

Mortality at six and nine months of follow-up according to dose of vitamin A supplementation for children aged 6 months to 5 years, Guinea-Bissau, November 2002-September 2003. Mortality rate ratios are shown with 95% confidence intervals

Dose	Boys	Girls	All
<b>At 6 months (deaths/years at risk)</b>			
Recommended	0.009 (6/636)	0.025 (15*/597)	0.017 (21/1233)
Half recommended	0.020 (12/602)	0.005 (3/597)	0.013 (15/1199)
Mortality rate ratio (half <i>v</i> full dose)†	1.98 (0.74 to 5.29)	0.19 (0.06 to 0.66)	0.69 (0.36 to 1.35)
<b>At 9 months (deaths/years at risk)</b>			
Recommended	0.014 (13/932)	0.023 (20*/877)	0.018 (33/1809)
Half recommended	0.017 (15/884)	0.007 (6/877)	0.012 (21/1761)
Mortality rate ratio half <i>v</i> full dose)†	1.14 (0.54 to 2.41)	0.28 (0.11 to 0.70)	0.62 (0.36 to 1.06)

\*Excludes one death caused by car crash.

†Adjusted for age group at intervention.

**What is already known on this topic**

Vitamin A supplementation to children aged >6 months reduces all cause mortality by 23% to 30% in low income countries

WHO recommends supplementation with vaccination, at 100 000 IU for infants aged 6-11 months and 200 000 IU for those aged ≥ 12 months

**What this study adds**

Half the dose currently recommended by WHO may provide equally good or better protection against mortality, but not against morbidity

the dose rather than the recommended dose was associated with more diarrhoea (incidence rate ratio 1.14, 1.01 to 1.28), fever (1.09, 0.99 to 1.20), and consultations at a hospital or health centre (1.10, 0.95 to 1.27). This tendency was similar in boys and girls.

The 1494 children who were at home at the nine month follow-up visit had their mid-upper arm circumference measured. There was no difference between those who received full versus half the recommended dose in boys or girls. Likewise using data from the routine registration of children < 3 years, there was no difference in mid-upper arm circumference related to the different doses of vitamin A.

**Discussion**

Half the recommended dose of vitamin A supplementation given with oral polio vaccine provides equally good or possibly better protection against mortality, at least in girls, and is most pronounced among children aged 18-60 months. The small difference in baseline distribution of age groups, with slightly more young infants in the group that received half the recommended dose, should not have confounded the results as we adjusted for this in the analysis.

We carried out the present study because two previous studies had suggested that the lower dose had a better effect on mortality<sup>5</sup> and morbidity.<sup>6</sup> Though not significant, our results are consistent with those from the previous study of mortality<sup>5</sup> and support the possibility that a smaller dose is better than the currently recommended dose of vitamin A supplementation. Our results suggest that the effect of dose on mortality differs for boys and girls. This has not been studied before.

It is important to note that mortality was low in children who took part in this study (annual mortality 0.015). Even the rate of 0.023 for girls in the high dose group was lower than the rates found before the oral polio and vitamin A campaigns started in 1999. Hence, the high dose of vitamin A did not increase mortality for girls but a low dose might have had a particularly beneficial effect when given together with oral polio vaccination.

**Other studies**

The effects of supplementation might not be mediated merely through prevention or treatment of vitamin A deficiency, as supported by several other observations.<sup>4</sup>

Different effects on mortality in boys and girls have been observed previously. The first large vitamin A trial reported that mortality increased in girls aged 0-11 months after supplementation whereas in boys it was reduced.<sup>7</sup> Two studies of vitamin A supplementation at birth have both indicated a more beneficial effect in boys.<sup>8,9</sup> An Indonesian study found better effect on morbidity with a lower dose of vitamin A.<sup>6</sup> In our study there was no differential mortality effect of dose in the group aged 6-18 months. In this age group, however, children who received the lower dose had greater morbidity. Several trials have reported a paradoxical overall beneficial effect of vitamin A on mortality but no such effect on morbidity. The explanation for this seemingly differential effect remains unknown.

Contributors: See bmj.com

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Competing interests: None declared.

Ethical approval: Ministry of Health's committee for research in Guinea-Bissau and the central ethical committee in Denmark.

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**Corrections and clarifications***Editor's Choice*

We omitted a vital "i" from the email address of one of the editors of the human and animal health theme issue (*BMJ* 2005;331, Editor's Choice, 26 Nov). The email address for Martin Alder (editor of the *Veterinary Record*) is editorial@bva-edit.co.uk.

*The parents' journey: continuing a pregnancy after a diagnosis of Patau's syndrome*

The reference (including the URL) at the end of this Clinical Review article by Louise Locock and colleagues is slightly wrong (*BMJ* 2005;331:1186-9, 19 Nov). The correct reference is: National Electronic Library for Health. Specialist Library Clinical Genetics. Patau Syndrome (<http://libraries.nelh.nhs.uk/genepool/viewResource.asp?uri=http%3A//libraries.nelh.nhs.uk/common/resources/%3Fid%3D93804&categoryID=7851>).