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% to 30% in low income countries. The beneficial effect is assumed to be due to the prevention of vitamin A deficiency. The World Health Organization recommends that supplements should be given when children are vaccinated. The currently recommended doses are 100 000 IU at age 6-11 months and 200 000 IU at age ≥12 months every 3-6 months.

The effect of supplementation may not be due exclusively to the prevention of vitamin A deficiency. For instance, there is no clear evidence that a large dose is better than a small dose, the tendency being the opposite in the two previous studies of different doses.

With the global effort to eradicate polio, national immunisation days with oral polio vaccine offer an additional opportunity to provide vitamin A. 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, 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 immunisation days were organised as two house-to-house campaigns lasting for one week each in October and November 2002. Staff from the health centres visited each house in a certain area to provide oral polio vaccination. In the study area, they were accompanied by assistants from the project. Each team was responsible for a subdistrict and brought the project’s census list for children aged <5 years in this particular district.

Protocol

During the second polio vaccination campaign in November 2002, vitamin A supplementation was offered to all children aged 6 months to 5 years. All the children also received the polio vaccine at the same time. Apart from such national immunisation 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 (MUAC), and diarrhoea, the hypothesis being that a lower dose would offer better protection against morbidity and mortality. We enrolled all eligible children. With about 6300 children aged 6-59 months and assuming that at least 85% took part in the campaign and participated in the study, we estimated that we need to enrol 5400 children to detect a 32% difference in the risk of admission to hospital and a 60% difference in mortality between the two treatments using a 5% significance level with 80% power. The study was explorative as we did not expect to be able to document a significant reduction in mortality.

Assignment

As most mothers were illiterate, we could obtain only verbal consent. The mothers were told that vitamin A was given because it reduces morbidity and mortality, but that there is no clear evidence which dose is the best. They were asked if their child could take part in the study. If they agreed, they had to draw a card from an envelope kept by the project assistant. All
Figure 1 shows the flow of children through the study. The large
envelopes had been prepared in advance by another project
assistance. Each envelope contained 100 cards, 50 marked “1” for
the full dose and 50 marked “2” for the half dose. According to
the result of the randomisation, vitamin A was given 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. If a mother did not want to take part in the study, the
child received the recommended dose and was not included in
the analyses. Slightly more children received the full dose of vita
min A, possibly because assistants classified a few children who
received the full dose elsewhere as having received it in the
present study. The only exclusion criterion was overt signs of
vitamin A deficiency, which was not present in any child.

Masking
Both assistants and mothers were aware which dose of vitamin A
the child received. The outcome assessment was done by other
assistants unaware of the hypotheses to be studied.

Participant flow and follow-up
Figure 1 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.

Using the project registration, we measured the effect of dose
for various health indicators, including mortality, admissions to
table, and mid-upper arm circumference. We carried out a
simple verbal autopsy with focus on main symptoms for all chil-
dren who died, allowing us to distinguish between deaths
probably caused by infectious diseases (typically symptoms of
fever, vomiting, diarrhoea, rapid respiration) 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. After nine months all children enrolled in the
study were visited to obtain information on mortality, admissions
to hospital, and mid-upper arm circumference. A total of 178
children moved during the nine months (95 received
recommended dose, 83 half this dose) and were censored from
the day they moved. Data were double entered.

For children less than 18 months old at the time of supplemen-
tation project assistants visited their homes every
month to collect information on diarrhoea and fever during the
past week and consultations at a health centre and hospital dur-
ing the past month. At about one third of the home visits, the
children were not seen because the mother and child were trav-
ell, or at the market. The numbers of missing children were
similar in the two groups (data not shown).

Statistical analysis
We analysed data on survival in Cox proportional hazard mod-
els with age as the underlying time, presenting results for both six
and nine months of follow-up. We censored data on one girl in
the high dose group who died in a car crash. We analysed data on
admission to hospital after vitamin A supplementation in Cox
proportional hazard models with age as the underlying time and
robust standard errors to adjust for repeated admissions. Differe-
ces in hospital case fatality were assessed with Mantel-
Haenszel methods.

As we had the morbidity data (yes/no) in one month
intervals, we analysed these data using discrete time survival
models. We used a complementary log-log regression model, which
can be viewed as a discrete time version of the Cox model.
We controlled for multiple morbidity episodes for each child
using generalised estimating equations. The correlation
within the child was modelled with an exchangeable correlation
structure. We used SAS version 8.2 except for morbidity analyses,
when we used the Stata 8.2 command xtcloglog.

Results
At baseline, there were slightly more infants aged 6-11 months
in the group that received the smaller dose (16% vs 12%). Otherwise,
the two randomisation groups were comparable with regard to
distribution of sex, maternal education, maternal age, siblings,
nutritional status, ethnicity, district, and socioeconomic indica-
tors (electricity in house and type of roof) (table 1). Age group
was the only risk factor that changed the main result 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 2). Post hoc subgroup analyses showed a
highly significant inversion of the effect for boys and girls
(P = 0.004 for homogeneity). While the lower dose was clearly
better for girls (mortality ratio 0.19, 95% confidence interval 0.06
to 0.60), the full dose might have been slightly better for boys
(table 2). 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
(data not shown). 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 (table 3).
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

Deaths at 6 and 9 months
Table 1 Baseline characteristics according to dose of vitamin A supplementation for children aged 6 months to 5 years, Guinea-Bissau, November 2002-September 2003. Figures are numbers (percentages) of children*

<table>
<thead>
<tr>
<th></th>
<th>Recommended dose (n=2525)</th>
<th>Half dose (n=2458)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1201 (43)</td>
<td>1234 (50)</td>
</tr>
<tr>
<td>Female</td>
<td>1224 (48)</td>
<td>1224 (50)</td>
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<tr>
<td>Age group at intervention (months):</td>
<td></td>
<td></td>
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<tr>
<td>6-11</td>
<td>302 (12)</td>
<td>383 (16)</td>
</tr>
<tr>
<td>12-17</td>
<td>345 (13)</td>
<td>322 (13)</td>
</tr>
<tr>
<td>18-35</td>
<td>962 (38)</td>
<td>963 (39)</td>
</tr>
<tr>
<td>36-60</td>
<td>916 (36)</td>
<td>790 (32)</td>
</tr>
<tr>
<td>Maternal education (years of schooling):</td>
<td></td>
<td></td>
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<tr>
<td>&lt;5</td>
<td>629 (27)</td>
<td>616 (28)</td>
</tr>
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<td>5-6</td>
<td>534 (23)</td>
<td>484 (22)</td>
</tr>
<tr>
<td>&gt;7</td>
<td>884 (38)</td>
<td>866 (39)</td>
</tr>
<tr>
<td>Maternal age (years):</td>
<td></td>
<td></td>
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<tr>
<td>&lt;20</td>
<td>435 (18)</td>
<td>386 (17)</td>
</tr>
<tr>
<td>20-24</td>
<td>787 (33)</td>
<td>774 (34)</td>
</tr>
<tr>
<td>25-29</td>
<td>566 (23)</td>
<td>639 (28)</td>
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<tr>
<td>≥30</td>
<td>499 (21)</td>
<td>510 (22)</td>
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<tr>
<td>Siblings:</td>
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<tr>
<td>&lt;1</td>
<td>865 (34)</td>
<td>821 (33)</td>
</tr>
<tr>
<td>2</td>
<td>1036 (41)</td>
<td>1017 (41)</td>
</tr>
<tr>
<td>≥4</td>
<td>624 (25)</td>
<td>620 (25)</td>
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<tr>
<td>Arm circumference at last visit before vitamin A (mm):</td>
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<td></td>
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<tr>
<td>&lt;110 mm</td>
<td>77 (30)</td>
<td>78 (31)</td>
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<tr>
<td>≥110 mm</td>
<td>1321 (95)</td>
<td>1373 (95)</td>
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<tr>
<td>Ethnicity:</td>
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<tr>
<td>Pueblo</td>
<td>924 (37)</td>
<td>920 (37)</td>
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<tr>
<td>Other</td>
<td>1601 (63)</td>
<td>1538 (63)</td>
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<td>District:</td>
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<td></td>
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<tr>
<td>Belem/Mindara</td>
<td>1769 (70)</td>
<td>1750 (71)</td>
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<tr>
<td>Electricity in household:</td>
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<td></td>
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<tr>
<td>Yes</td>
<td>703 (28)</td>
<td>637 (27)</td>
</tr>
<tr>
<td>No</td>
<td>1764 (72)</td>
<td>1764 (73)</td>
</tr>
<tr>
<td>Roof type:</td>
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<td></td>
</tr>
<tr>
<td>Zinc</td>
<td>2228 (89)</td>
<td>2142 (89)</td>
</tr>
<tr>
<td>Straw</td>
<td>240 (10)</td>
<td>261 (11)</td>
</tr>
</tbody>
</table>

*Numbers do not always add up to total because of missing data.

(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 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) (fig 2). This tendency was similar in boys and girls (data not shown).

The 1494 children who were at home at the nine month follow-up visit had the mid-upper arm circumference measured. There was no difference in this between those who received full versus half the recommended dose in boys or girls (data not shown). 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 (data not shown).

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 and morbidity. Our study was not large enough to document a reduction in mortality, and the mortality fell during the trial making it more difficult to document a significant effect. Though not significant, our results are consistent with those from the previous study of mortality and support the possibility that a smaller dose might be better than the currently recommended dose of vitamin A supplementation.

The WHO study

The previous study of mortality was a WHO multicentre placebo controlled study of vitamin A supplementation with routine immunisations in infancy. The children in the vitamin A group received 25 000 IU of vitamin A with each of the first three diphtheria, tetanus, and pertussis (DTP) and polio vaccines at 6, 10, and 14 weeks of age. At the age of 9 months, with measles vaccination, infants in the vitamin A group were given a further dose of 25 000 IU, and those in the control group received 100 000 IU vitamin A. There was no difference in mortality after the first three doses of vitamin A between the two groups, and there was no difference in vitamin A status at 9 months of age, when the infants received measles vaccine and additional supplementation. Between 9 and 12 months of age, however, when follow-up was terminated, the group who received only 25 000 IU of vitamin A with measles vaccine had substantially lower mortality (mortality ratio = 0.42, 0.21 to 0.85) than the control children who received the recommended dose of 100 000 IU. Though the WHO study was not designed to examine the effect of different doses of vitamin A on mortality, it did suggest, as did our study, that a lower dose is better.

Our results suggest that the effect of dose on mortality differs for boys and girls. This has not been studied before. The other health indicators we examined—admissions to hospital, arm circumference, and morbidity—did not indicate significant effects of low dose, though the case fatality in hospital was consistent with a beneficial effect of low dose for girls.

It is important to note that mortality was low in children who took part in this (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 consistent mortality results of a low dose of vitamin A indicate that the effects of supplementation might not be mediated merely through prevention or treatment of vitamin A deficiency. As argued elsewhere, this notion is supported by several other observations: different effect on mortality in boys and girls have been observed previously. In the first large vitamin A trial, Sommer et al reported that mortality increased in girls aged 0-11 months after supplementation whereas in boys it was reduced. Two studies of vitamin A supplementation at birth have both indicated a more beneficial effect in boys. With regard to morbidity, an Indonesian study of the effect on morbidity and growth of either 25,000 or 50,000 IU vitamin A or placebo given with the three doses of DTP vaccines found better effect on morbidity of the lower dose. 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 more diarrhoea and fever and were seen more often at the health centre or the hospital. 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: CSB, CM, AR, IML, and PA planned the study. CM was responsible for the data collection, CSB, PA, and HJ analysed the data. CSB wrote the first draft of the paper and all authors contributed to the final version. CSB and PA are guarantors.

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**Table 3** Admission to hospital* and hospital case fatality at six and nine months of follow-up according to dose of vitamin A supplementation for children aged 6 months to 5 years of age, Guinea-Bissau, November 2002-September 2003. Admission rate ratios are shown with 95% confidence intervals.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Boys</th>
<th>Girls</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Admission rate</td>
<td>Deaths/ admissions</td>
<td>Admission rate</td>
</tr>
<tr>
<td>At 6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommended</td>
<td>0.049</td>
<td>4/91</td>
<td>0.046</td>
</tr>
<tr>
<td>Half recommended</td>
<td>0.057</td>
<td>5/34</td>
<td>0.039</td>
</tr>
<tr>
<td>Admission rate ratio (half v full dose)</td>
<td>1.11 (0.68 to 1.81)</td>
<td>0.83 (0.48 to 1.45)</td>
<td>0.98 (0.68 to 1.41)</td>
</tr>
<tr>
<td>At 9 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommended</td>
<td>0.052</td>
<td>4/48</td>
<td>0.049</td>
</tr>
<tr>
<td>Half recommended</td>
<td>0.052</td>
<td>4/48</td>
<td>0.037</td>
</tr>
<tr>
<td>Admission rate ratio (half v full dose)</td>
<td>0.98 (0.64 to 1.44)</td>
<td>0.74 (0.47 to 1.18)</td>
<td>0.85 (0.63 to 1.16)</td>
</tr>
</tbody>
</table>

*Admissions/years at risk
†Adjusted for age group at intervention.

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**Fig 2** Morbidity measured by consultations at hospital or health centre within nine months of follow-up after vitamin A supplementation for children aged 6-18 months at time of supplementation, Guinea-Bissau, November 2002-September 2003.


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