Two Different Doses of Supplemental Vitamin A Did Not Affect Mortality of Normal-Birth-Weight Neonates in Guinea-Bissau in a Randomized Controlled Trial1,2

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Abstract

Whether neonatal vitamin A supplementation (NVAS) should be policy in areas with vitamin A deficiency is debated. We observed that a smaller dose of vitamin A may decrease mortality more than a larger dose and conducted a randomized, double-blind, placebo-controlled trial in Guinea-Bissau with the primary aim of comparing the effect of 50,000 with 25,000 IU neonatal vitamin A on infant mortality. The secondary aim was to study the effect of NVAS vs. placebo, including a combined analysis of NVAS trials. Between 2004 and 2007, normal-birth-weight neonates were randomly assigned in a 1:1:1 ratio to be administered 2 different doses of vitamin A (50,000 or 25,000 IU) or placebo. Infant mortality rates (MRs) were compared in Cox models providing MR ratios (MRRs). Among 6048 children enrolled, there were 160 deaths in 4125 person-years (MR = 39/1000). There was no difference in mortality between the 2 dosage groups: the MRR for 25,000 vs. 50,000 IU was 0.96 (95% CI: 0.67, 1.38). Neither dose of NVAS was associated with lower mortality than placebo (MRR = 1.28; 95% CI: 0.91, 1.81). In a combined analysis of the present trial and 2 previous NVAS trials in Guinea-Bissau, the effect of receiving NVAS (any dose) vs. placebo was 1.13 (95% CI: 0.94, 1.36) and differed significantly (P = 0.01) between boys (0.80; 95% CI: 0.58, 1.09) and girls (1.35; 95% CI: 1.04, 1.75). We could not confirm that a smaller dose of neonatal vitamin A reduces mortality more than a larger dose. We confirmed 2 other trials in Guinea-Bissau that showed no beneficial effect of NVAS. This trial was registered at clinicaltrials.gov as NCT00168610. J. Nutr. 144: 1474–1479, 2014.

Introduction

Vitamin A deficiency is widespread in low-income countries, and vitamin A supplementation (VAS)6 of 6-mo-old to 5-y-old children may reduce overall mortality substantially as demonstrated by several randomized controlled trials in the late 1980s and early 1990s (1). Most of the trials used high-dose supplements. However, the trial that reported the largest mortality reduction used small weekly dosing (2). In Guinea-Bissau we conducted a randomized controlled trial, comparing the effect of half the recommended dose of vitamin A with the recommended dose given to 6-mo-old to 5-y-old children during a national campaign (3). The lower dose was associated with larger reductions in overall mortality than the higher dose, and significantly so in girls (3).

Several trials have been carried out to study whether it is possible to extend the beneficial effect of VAS seen in children >6 mo of age to younger children. Most of the studies providing VAS to children between 1 and 5 mo of age found no effect or a tendency for a negative effect (4). In neonates, the evidence regarding the effect of VAS on mortality is conflicting (5). In Guinea-Bissau, we conducted a trial of neonatal VAS (NVAS), comparing a dose of 50,000 IU with placebo in normal-birth-weight neonates from 2002 to 2005 (VITA I) (6). When recruitment for VITA I had ended and while follow-up was ongoing, we took advantage of the existing set-up to initiate the present trial with the primary objective to compare the mortality effect of 2 different doses of vitamin A in normal-birth-weight neonates.

We randomly assigned children to be administered 50,000 IU [as used in the previous NVAS trials (6–8)], 25,000 IU, or placebo as a single dose at birth. Our a priori hypothesis was

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3 Research Center for Vitamins and Vaccines (CVIVA), Bandim Health Project, Statens Serum Institutt, Copenhagen, Denmark; 4 Bandim Health Project, INDEPTH Network, Bissau, Guinea-Bissau; and 5 Odense Patient data Explorative Network, Institute of Clinical Research, University of Southern Denmark/Odense University Hospital, Odense, Denmark

4 Abbreviations used: BCG, bacille Calmette-Guérin; DTP, diphtheria-tetanus-pertussis; RBP, retinol-binding protein; VAS, vitamin A supplementation.

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that a dose of 25,000 IU would be associated with larger mortality reductions than a dose of 50,000 IU. As a secondary objective, we aimed to study the effect of NVAS vs. placebo, including a combined analysis of VITA I and the present trial. We prespecified that we would conduct all analyses stratified by sex. New results that became available during the conduct of the trial indicated possible interactions between NVAS and season (6), ponderal index (6), and vaccination status (9). Hence, we also examined these possible interactions in the present study.

Participants and Methods

Trial design

This trial was a double-blind, placebo-controlled randomized trial enrolling healthy normal-birth-weight neonates (>2500 g). Infants were randomly assigned in a 1:1:1 ratio to 3 different treatment groups: 50,000 IU of vitamin A, 25,000 IU of vitamin A, or placebo, concurrent with bacille Calmette-Guérin (BCG) vaccination.

Setting

The Bandim Health Project has a demographic surveillance system in 6 suburban districts of the capital of Guinea-Bissau covering ~102,000 inhabitants. There are 3 health centers in the study area, 1 of which has a maternity ward. The national hospital where many women from the study area give birth is a few kilometers away. Bandim Health Project assistants are placed at the health centers and the hospital to register all study area children when they are born and when they come for vaccinations. All houses in the study area are visited monthly to register new pregnancies and births. All children are routinely followed with home visits every 3 mo until 3 y of age. Enrollment into the trial took place between 29 November 2004 and 31 May 2007.

Local vitamin A status. Guinea-Bissau is classified as having subclinical vitamin A deficiency by UNICEF (10). Almost all children in the study area are breast-fed to at least 18 mo of age. Within VITA I we collected blood samples from subgroups of children at 6 wk and 4 mo of age; at 4 mo of age, plasma was also collected from the mothers (11). The plasma was analyzed for retinol-binding protein (RBP) and C-reactive protein. Overall, NVAS had no effect on RBP concentrations at 6 wk and 4 mo of age (11). Controlled for C-reactive protein, the prevalence of having RBP corresponding to values <0.7 μmol/L retinol (i.e., low RBP) was 27% at age 6 wk and 9% at age 4 mo (11). One mother had low RBP (11).

During the period in which this trial was conducted, the frequency of national NVAS campaigns increased from 1 to 2 per year; there were campaigns in December 2004, December 2005, May 2006, November 2006, July 2007, and December 2007 during which children between 6 mo and 5 y of age were offered NVAS. The last child was enrolled in the present trial on 31 May 2007. In August 2007, we initiated a NVAS trial with random assignment to NVAS or placebo at the first vaccination contact after 6 mo of age. At that time we asked for ethical approval to end follow-up for the remaining children in the present trial at the time of the next NVAS campaign occurring 14 December 2007.

Local vaccination schedule. During the trial period, Guinea-Bissau followed the WHO recommendations of providing BCG and oral polio vaccine at birth; combined diphtheria-tetanus-pertussis (DTP) vaccine and oral polio vaccine at ages 6, 10, and 14 wk; and measles vaccine at age 9 mo. However, an early measles vaccination trial was conducted including children born between March 2003 and 14 October 2006. Children were enrolled at age 4.5 mo, provided they had been administered all 3 doses of DTP vaccine at least 4 wk before enrollment. At enrollment, the children were randomly assigned in a 1:2 ratio to early measles vaccine or to no early measles vaccine. All children were invited back for the recommended measles vaccine at age 9 mo (12).

Local HIV situation. While we conducted the trial, the prevalence of HIV-1 was ~3–5% in the study area among women of childbearing age (13). A large proportion of pregnant women were screened for HIV to prevent vertical transmission. With the vertical-transmission control program ongoing, we expect <1% of the children to be HIV-1 infected.

Participants and recruitment

Eligible participants were healthy normal-birth-weight neonates who were due to be administered BCG vaccine. Mothers giving birth at the maternity wards were invited to participate when their child was to be administered BCG vaccination before discharge. Mothers who delivered at home were invited to participate when they came for BCG vaccination at the 3 health centers in the study area. Exclusion criteria were weight <2500 g at presentation or overt illness/malformations.

Mothers were informed by a trained field worker about the trial and asked if they wanted their child to participate. If the mothers wished to participate, they were asked to sign or fingerprint the consent form.

Randomization and interventions

At each inclusion site, the randomization procedure was carried out by a centrally trained assistant every day except during short vacations. After providing consent, the mother drew a lot from an envelope. Each envelope was prepared by the data manager, who did not take part in the enrollment procedures, and contained 48 folded lots indicating from which of 3 numbered bottles—“3,” “4,” or “5”—the child should receive his or her supplement. The result of the randomization was noted on the inclusion form and the lot was also stapled on the inclusion form. In accordance with the result of the randomization, a trained nurse slowly released 0.5 mL oil from bottle 3, 4, or 5 into the mouth of the child with a sterile syringe (i.e., either 50,000 or 25,000 IU vitamin A or placebo).

The vitamin A and placebo preparations were stored in dark glass bottles, which were prepared at Skanderborg Pharmacy, Denmark, and contained 20 doses of 0.5 mL of vegetable oil. One-third of the bottles had a concentration of 50,000 IU vitamin A as retinyl palmitate and 10 IU vitamin E per 0.5 mL oil, one-third of the bottles contained 25,000 IU vitamin A as retinyl palmitate and 10 IU vitamin E per 0.5 mL oil, and the last third had only 10 IU vitamin E per 0.5 mL oil. The bottles were kept at 5°C. A fresh lot was prepared at least once a year. Under such circumstances the stability is very high (14). After the trial had ended, 1 set of bottles was tested by Vitas Analytical Pharma Services in Oslo, Norway; concentrations were 104,210 IU/mL in the first bottle, 55,233 IU/mL in the second bottle, and 0 IU/mL in the third bottle. Apart from the randomization number the bottles looked alike, and small differences in taste and color of the contents were judged as being unimportant due to the recipients’ age. The code was kept at the pharmacy until follow-up had ended.

Outcome measures

The outcome was infant mortality. All children were followed through the routine registration system every 3 mo and were visited by a special team at age 12 mo to assess vital status. The registration system assistants and the special team were unaware of the allocated treatment, because they were not present during enrollment, and the information was not transferred to the children’s vaccination card or follow-up forms. Deaths were registered at each visit and followed by a verbal autopsy report conducted by a trained local physician. On the basis of the verbal autopsy report, whether the death was accidental or not was assessed.

Sample size

In our previous study of different doses of VAS, we observed a 38% mortality difference after 9 mo of follow-up (3). For our primary objective, a sample size of 2000 per group was chosen to detect a 30% mortality difference with 80% power and 5% significance between the 25,000- and 50,000-IU groups assuming a mortality rate (MR) of 70/1000 in the 50,000-IU group. For our secondary objective, this sample size would allow us to detect a 23% reduction in mortality from receiving 50,000 IU of vitamin A compared with placebo.

Statistical analysis

All analyses were conducted by using Stata 12.1 (StataCorp) with a significance level set at P < 0.05. Survival was assessed in Cox proportional hazards models providing MR ratios (MRRs). We used age as the underlying time; hence, age was inherently controlled for. Infants contributed person-years at risk from enrollment until whichever of the following came first: they reached the age of 12 mo, they received their 12-mo visit by our special team a few days before their first birthday; they moved, they died, or at the end of follow-up on 14 December 2007. Deaths due to accidents were
censored \((n = 2); \text{Fig. 1}\). We conducted an overall intention-to-treat analysis, but because subsequent administration of vitamin A could modify the effect of the original intervention \((15)\), we conducted all following analyses with censoring at the time point of the first national VAS campaign occurring after an infant had turned 6 mo of age. We did that irrespective of whether the child was registered to have received VAS in the campaign or not, because coverage was high in many campaigns, and we could have introduced selection bias by censoring follow-up only for participating children. Thirty-one children born after 1 January 2007 were enrolled in a new VAS trial initiated August 2007 before they had reached 12 mo of age and were censored at the date of enrollment into the new trial. None of these children died before 14 December 2007.

**Primary and secondary objectives.** We first compared the effect of the 2 different doses of vitamin A against each other, overall, and stratified by sex. For our secondary objective, we envisaged providing a combined estimate of \(50,000\) IU vitamin A in the present trial and the previous VITA I. Because there was no difference between the 2 doses of NVAS in the present trial, we also assessed the effect of any dose of NVAS vs. placebo in the present trial as well as in a combined analysis of the present trial and VITA I. The analyses were conducted overall and by sex. The analysis was also limited to children supplemented within the first 48 h of life.

**Post hoc analyses.** To test the findings from VITA I, we examined the possible interactions between NVAS and season, ponderal index, and vaccination status. As in VITA I, we defined rainy season from June to November, and we only calculated ponderal index in the children who were enrolled during the first 2 d of life (for whom a valid birth weight was available) and compared the effect of NVAS in the 3 highest quartiles with the effect of NVAS in the lowest quartile of ponderal index \((6)\). As in previous studies, the effect of NVAS by vaccination status was investigated by examining children in the time window of BCG vaccine (from inclusion and until the first DTP vaccine was administered or the child reached 6 wk of age, the age of the first DTP vaccine) and the time window of DTP vaccine (from the date of registration of the first DTP vaccine and until the child reached age 9 mo or was administered the measles vaccine in the early measles vaccine trial or the routine measles vaccine scheduled at age 9 mo) \((9)\). Effect modification was analyzed by investigating the homogeneity of the effect of NVAS over the different categories of the suspected modifier by using Wald test statistics.

**Combined analyses.** Because more trials of NVAS have been completed, we conducted a combined analysis of all NVAS trials in Guinea-Bissau: the present trial, VITA I in normal-birth-weight neonates \((6)\), and a trial conducted between 2004 and 2008 in low-birth-weight neonates \((VITA II)\) \((16)\). Combined analyses were conducted by using the "meta" command in Stata. Random-effect estimates are presented.

**Ethical considerations**

The protocol was approved by the Ministry of Health in Guinea-Bissau, and the Danish Central Ethical Committee gave its consultative approval \((2004-7041-19)\). All children were offered free consultations and essential drugs if the child became ill, and all children were offered VAS by our team at the home visit at 12 mo of age.

**Results**

Of 6053 children invited to participate, 6048 were randomly allocated to each of the 3 groups \((50,000\) IU vitamin A, \(25,000\) IU vitamin A, or placebo) \((Fig. 1)\). The 3 randomly assigned groups were similar in terms of their background characteristics \((Table 1)\). A total of 176 deaths occurred; 2 of these were due to accidents and were censored. Fourteen deaths occurred after the child had been eligible for a national vitamin A campaign. Hence, censoring for accidents and subsequent VAS, the cohort had 160 deaths during 4125 person-years of risk, corresponding to an MR of 39 per 1000 person-years.

**Primary objective: effect of different doses of vitamin A.** Overall, there was no difference in mortality between the groups that were administered \(25,000\) or \(50,000\) IU vitamin A; hence, there was no indication that the smaller dose was associated with larger mortality reductions than a larger dose, with the MRR comparing \(25,000\) with \(50,000\) IU being \(0.96\) \((95\%\ CI: 0.67, 1.38)\). In the intention-to-treat analysis without censoring for...
subsequent VAS, the MRR was 0.97 (95% CI: 0.68, 1.38). There was no evidence that the smaller dose was better for girls: the MRR comparing 25,000 with 50,000 IU was 1.21 (95% CI: 0.70, 2.08) in girls and 0.79 (95% CI: 0.48, 1.30) in boys ($P$ for same effect in the 2 sexes = 0.26) (Table 2). The effect of receiving 50,000 IU vs. placebo was 1.31 (95% CI: 0.89, 1.93); the effect of 25,000 IU vs. placebo was 1.26 (95% CI: 0.85, 1.86) (Fig. 2A).

Secondary objective: effect of vitamin A vs. placebo. Because there were no differences between the 2 dosage groups, the groups were combined to evaluate the effect of NVAS (50,000 or 25,000 IU) on mortality. Compared with placebo, NVAS was not associated with lower infant mortality overall or in either sex (Table 2, Fig. 2B). Overall, the MRR was 1.28 (95% CI: 0.91, 1.81). If limited to children enrolled during the first 48 h, the MRR was 1.12 (95% CI: 0.73, 1.73). In the intention-to-treat analysis without censoring for subsequent VAS, the MRR was 1.15 (95% CI: 0.83, 1.59).

Post hoc analyses: exploring interaction identified in previous trials. In VITA I, we found interactions between NVAS and season, ponderal index, and vaccination status. In the present trial we could not confirm interactions between VAS and season (Table 3).

Combined analyses. In a combined analysis of this trial and VITA I, the MRR comparing 50,000 IU with placebo was 1.16 (95% CI: 0.91, 1.46). The MRR comparing any dose of VAS (50,000 or 25,000 IU) with placebo was 1.16 (95% CI: 0.92, 1.45).

In a combined analysis of all 3 trials from Guinea-Bissau, the present trial, VITA I in normal-birth-weight neonates (6), and VITA II in low-birth-weight neonates (16), the MRR comparing any dose of NVAS with placebo was 1.13 (95% CI: 0.94, 1.36; $P$ = 0.19) and was significantly different in boys (0.80; 95% CI: 0.58, 1.09) and girls (1.35; 95% CI: 1.04, 1.75), with a $P$ value for the same effect in boys and girls of 0.01.

Discussion
In the present randomized placebo-controlled trial we were not able to confirm our hypothesis that a small dose of vitamin A reduces mortality more than a large dose. As in previous NVAS trials, NVAS was significantly beneficial in the lowest quartile of ponderal index but not in the 3 highest; this differential effect was most pronounced in girls (Table 3). We could not confirm a negative effect of NVAS in girls in the DTP vaccine window (Table 3).

TABLE 1 Background characteristics at enrollment of children randomly assigned to 2 different doses of neonatal vitamin A or placebo

<table>
<thead>
<tr>
<th>Participants with information</th>
<th>50,000 IU (n = 2015)</th>
<th>25,000 IU (n = 2011)</th>
<th>Placebo (n = 2022)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys, %</td>
<td>6048</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td>Suburb, %</td>
<td>6047</td>
<td>60</td>
<td>45</td>
</tr>
<tr>
<td>Bandim</td>
<td>18</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Belém/Mindara</td>
<td>37</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>Maternal schooling, %</td>
<td>5380</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>No</td>
<td>61</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Yes</td>
<td>68</td>
<td>68</td>
<td>70</td>
</tr>
<tr>
<td>Maternal ethnicity, %</td>
<td>5907</td>
<td>30</td>
<td>29</td>
</tr>
<tr>
<td>Pepel</td>
<td>68</td>
<td>68</td>
<td>70</td>
</tr>
<tr>
<td>Other</td>
<td>5630</td>
<td>253 ± 30</td>
<td>251 ± 30</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>6048</td>
<td>3.3 ± 0.7</td>
<td>3.3 ± 0.7</td>
</tr>
<tr>
<td>Length, cm</td>
<td>6042</td>
<td>51 ± 3</td>
<td>51 ± 3</td>
</tr>
<tr>
<td>Mid-upper arm circumference, mm</td>
<td>6041</td>
<td>99 ± 10</td>
<td>99 ± 10</td>
</tr>
<tr>
<td>Ponderal index at birth, %</td>
<td>3255</td>
<td>26 ± 2</td>
<td>26 ± 2</td>
</tr>
<tr>
<td>Lowest quartile of ponderal index at birth, %</td>
<td>3255</td>
<td>26</td>
<td>23</td>
</tr>
</tbody>
</table>

1 Values are means ± SDs or percentages of all children unless otherwise indicated.
2 Some children had no information for this category.
3 Calculated only for children enrolled in the first 2 d after delivery.

TABLE 2 Effect of different doses of neonatal vitamin A supplementation on infant mortality

<table>
<thead>
<tr>
<th>MR (deaths/person-years)</th>
<th>50,000 IU vitamin A</th>
<th>25,000 IU vitamin A</th>
<th>Placebo</th>
<th>Placebo vs. 50,000 IU vitamin A</th>
<th>Placebo vs. 25,000 IU vitamin A</th>
<th>Any dose of vitamin A vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>43 (55/1373)</td>
<td>41 (56/1366)</td>
<td>33 (45/1377)</td>
<td>0.96 (0.67, 1.38)</td>
<td>1.28 (0.91, 1.81)</td>
<td></td>
</tr>
<tr>
<td>By sex</td>
<td>50,000 IU vitamin A</td>
<td>25,000 IU vitamin A</td>
<td>Placebo</td>
<td>Placebo vs. 50,000 IU vitamin A</td>
<td>Placebo vs. 25,000 IU vitamin A</td>
<td>Any dose of vitamin A vs. placebo</td>
</tr>
<tr>
<td>Boys</td>
<td>50 (35/696)</td>
<td>39 (28/710)</td>
<td>33 (24/724)</td>
<td>0.79 (0.48, 1.30)</td>
<td>1.35 (0.84, 2.16)</td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>35 (24/882)</td>
<td>43 (28/857)</td>
<td>32 (21/853)</td>
<td>1.21 (0.70, 2.08)</td>
<td>1.21 (0.73, 2.01)</td>
<td></td>
</tr>
<tr>
<td>$P$ for same effect by sex</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.26</td>
<td>0.75</td>
<td></td>
</tr>
</tbody>
</table>

1 MRR estimates were derived from Cox proportional hazards models. Follow-up was until 12 months of age or until the first vitamin A supplementation opportunity occurring after 6 months of age. MR, mortality rate; MRR, mortality rate ratio.
trials in Guinea-Bissau, we found no evidence for a beneficial effect of NVAS on infant survival. In a post hoc analysis we tested previous subgroup findings in the present trial. We did not confirm that NVAS had a more negative effect on survival in girls than in boys or that the effect was more negative after DTP vaccine and in the rainy season. We confirmed that NVAS has differential effects depending on the ponderal index of the child, improving survival in the smallest of these normal-birth-weight children.

Strengths and weaknesses. The trial was a randomized, double-blind, placebo-controlled trial. All trial procedures were already established in relation to the previous trial and all staff were well trained. When we initiated the present trial, follow-up of the previous trial was still ongoing and blinded. We had based our sample size calculations on an infant mortality rate of 70, but in this trial it declined to 39. Although this clearly is a very positive development, it decreased our power to detect any differences between the randomly assigned groups. With the current MR, we only would have been able to show a difference of >40% between the 2 doses. Because there was minimal difference between the 2 doses, we used the data to test findings made in our previous NVAS trial. All of these analyses were not a priori analyses prespecified in the protocol but were formulated before we initiated the data analysis of the present trial. The trial was not sized to test these findings, and the results should be interpreted with appropriate caution. The 3 Guinean NVAS trials showed quite similar effects, and it was therefore justified to combine them; however, it should be noted that they were conducted in different study populations (low-birth-weight and normal-birth-weight) and the underlying MR differed between studies.

Interpretation. There is now clear evidence that NVAS provides no overall benefit on survival in Guinea-Bissau, at least not for girls, irrespective of dose. We could not confirm our previous findings of a sex-differential effect of NVAS in the present trial, but a sex-differential effect was still present in a meta-analysis of all 3 trials from Guinea-Bissau. As in our previous studies, there was a slight tendency for a negative effect in girls who had DTP as their most recent vaccine.

We did not measure vitamin A status in the present trial. However, data from other studies in the area indicate that, despite the fact that almost all children are breast-fed, vitamin A deficiency is common in Guinea-Bissau, equally among boys and girls (11,17). In VITA I, the MRR of VAS vs. placebo was

![Figure 2](https://academic.oup.com/jn/article-abstract/144/9/1474/4575064)

**TABLE 3** Effect of neonatal vitamin A supplementation compared with placebo on infant mortality by potential effect modifiers

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MR (deaths/person-years)</strong></td>
<td>Vitamin A</td>
<td>Placebo</td>
<td>MRR (95% CI)</td>
</tr>
<tr>
<td>By season</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rainy season</td>
<td>41 (42/1031)</td>
<td>39 (20/517)</td>
<td>1.04 (0.61, 1.78)</td>
</tr>
<tr>
<td>Dry season</td>
<td>43 (73/1713)</td>
<td>29 (25/860)</td>
<td>1.47 (0.94, 2.32)</td>
</tr>
<tr>
<td><strong>P</strong> for same effect by season</td>
<td>0.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>By ponderal index²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three highest quartiles</td>
<td>48 (55/1137)</td>
<td>29 (17/578)</td>
<td>1.64 (0.95, 2.82)</td>
</tr>
<tr>
<td>Lowest quartile</td>
<td>30 (11/363)</td>
<td>70 (13/185)</td>
<td>0.43 (0.19, 0.96)</td>
</tr>
<tr>
<td><strong>P</strong> for same effect by ponderal index</td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>By vaccination status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCG window</td>
<td>111 (41/368)</td>
<td>87 (16/183)</td>
<td>1.28 (0.72, 2.29)</td>
</tr>
<tr>
<td>DTP window</td>
<td>25 (45/1780)</td>
<td>24 (22/901)</td>
<td>1.04 (0.62, 1.72)</td>
</tr>
<tr>
<td><strong>P</strong> for same effect</td>
<td>0.60</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ MRR estimates were derived from Cox proportional hazards models. Follow-up was until 12 months of age or until the first vitamin A supplementation opportunity occurring after 6 months of age. BCG, bacille Calmette-Guérin; DTP, diphtheria-tetanus-pertussis; MR, mortality rate; MRR, mortality rate ratio.

² Subgroup that was enrolled during the first 2 d of life.
0.69 (95% CI: 0.34, 1.38) in infants with a ponderal index in the lowest quartile compared with 1.35 (95% CI: 0.86, 2.13) in other children (P-interaction = 0.11) (6). This observation was confirmed in the present trial. This may reflect that the smaller children are more vitamin A deficient (18) and benefitted more from VAS. However, it should be noted that in VITA II we found no beneficial effect of NVAS to Guinean children with low birth weight, who would presumably be even more vitamin A deficient (16). Hence, the effect of NVAS does not seem to be directly correlated with the level of vitamin A deficiency.

Comparison with other vitamin A trials. Since we first found that a lower dose was more beneficial than a higher dose in children >6 mo old (3), we have had an opportunity to repeat the trial. We were not able to confirm that a smaller dose was associated with larger reductions in mortality than the larger dose (19). This may have been related to the fact that in the second trial many children had received VAS on a previous occasion (19); 2 studies have now found that previous VAS may prime a better response to a subsequent dose of vitamin A (15,20). Taken together, the total body of evidence does not support that a lower dose of VAS is more beneficial than a higher dose; however, nor does a higher dose seem to provide more benefits than a lower dose.

Apart from our NVAS trials from Guinea-Bissau, only 1 other trial of NVAS was conducted in Africa; it showed, if anything, a tendency for a negative effect for children born to both HIV-negative (21) and HIV-positive (22) women. Currently, 2 NVAS trials are ongoing in rural Africa, in Ghana and Tanzania, to test whether NVAS at a dose of 50,000 IU is associated with a 15% reduction in infant mortality before 6 mo of age. Even if NVAS is associated with benefits in these trials, it would be difficult to recommend it as a general policy in Africa because it is associated with increased mortality in some situations.

Conclusions. Children did not have lower mortality if they were administered a lower rather than a higher dose of neonatal vitamin A; there was no difference between receiving 50,000 or 25,000 IU vitamin A. We confirmed 2 other trials that showed no overall beneficial effect of NVAS in Guinea-Bissau.

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