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Interventions

# The effect of neonatal vitamin A supplementation on morbidity and mortality at 12 months: a randomized trial

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## Abstract

**Background**: Neonatal vitamin A supplementation (NVAS) is an intervention hypothesized to reduce infant morbidity and mortality. The objective of this study was to assess the efficacy of neonatal vitamin A supplementation in reducing infant morbidity and mortality and assess potential sources of heterogeneity of the effect of NVAS.

**Methods**: We completed an individually randomized, double-blind, placebo-controlled trial in Tanzania. Infants were randomized within 3 days of birth to a single dose of vitamin A (50 000 IU) or placebo. We assessed infants at 1 and 3 days after supplementation, as well as 1, 3, 6 and 12 months after supplementation. We included all live births in the analysis and used relative risks (RR) and 95% confidence intervals (CI) to assess the risks of mortality and hospitalization by 12 months. We used general estimating equations to assess the incidence of morbidities during infancy.

**Results**: A total of 31 999 infants were enrolled in the study between August 2010 and March 2013. At 12 months, vitamin A did not reduce all-cause infant mortality (RR 1.04; 95% CI 0.92-1.16), nor affect hospitalization (RR 1.09; 95% CI 0.97-1.22) or all-cause morbidity (RR 1.00; 95% CI 0.96-1.05). Postpartum maternal vitamin A supplementation modified the effect of neonatal vitamin A supplementation on mortality at 12 months (*P*-value, test for interaction = 0.04). Among infants born to women who received a mega-dose of vitamin A after delivery, NVAS appeared to increase the risk of death (RR 1.12; 95% CI 0.98-1.29), whereas the risk of death among infants born to women who did not receive a mega-dose was reduced (RR 0.86; 95% CI 0.70-1.06). We noted no modification of the effect of NVAS by infant gender, birthweight or maternal HIV status.

**Conclusion**: NVAS did not affect the risk of death or incidence of common childhood morbidities. However, this study sheds light on potential sources of heterogeneity of the effect of neonatal vitamin A supplementation which should be further examined in a pooled analysis of all NVAS trials.

**Key words:** Neonatal vitamin A supplementation, infant mortality, hospitalization, morbidity, Tanzania

**Key Messages**

- The recent completion and analysis of the three largest neonatal vitamin A supplementation trials (NEOVITA) found conflicting results regarding the efficacy of this intervention in reducing infant morbidity and mortality. A meta-analysis combining these data with that of seven previous trials found important heterogeneity in mortality effects.
- Overall, we found no evidence that neonatal vitamin A supplementation in Tanzania reduces the risk of mortality, hospitalization or morbidity during infancy.
- Data from this trial suggest that maternal vitamin A status may modify the effect of neonatal vitamin A supplementation.

## Introduction

Despite improvements in child survival in the past four decades, an estimated 6.3 million children under the age of five died in 2013.[1] Although child mortality continues to decline, there has been slower progress in reducing infant mortality. Interventions to reduce neonatal and infant mortality are needed, and there is evidence that vitamin A supplementation can reduce morbidity and mortality among children aged 6 to 59 months.[2] A number of trials to assess the efficacy of neonatal vitamin A supplementation have had conflicting findings. Some trials have shown clear benefit associated with supplementation,[3,4] but others suggest a null or possibly harmful effect.[5,6] The reason for qualitative differences in the effect of neonatal vitamin A supplementation between these trials is not well understood.

The efficacy of neonatal vitamin A supplementation may be modified by baseline maternal or infant characteristics. A meta-analysis including all published trials to date[7] suggested that geographical region, which is highly correlated with the population prevalence of vitamin A deficiency, may explain the heterogeneity of trial results. Specifically, trials performed in Asia (also classified as having moderate or severe maternal vitamin A deficiency)[3,4,8–10] had a 13% reduced risk of mortality from supplementation to 6 months [relative risk (RR) 0.87; 95% confidence interval (CI) 0.78-0.96], whereas African trials (countries also classified as having mild or no maternal deficiency)[5,6,11–13] showed a 10% increased risk of mortality associated with neonatal vitamin A supplementation (RR 1.10; 95% CI 1.00-1.21). A trial in Guinea Bissau among normal birthweight infants (given 50 000 IU or 25 000 IU vitamin A) and a trial in Zimbabwe among HIV-infected women also found no effect of neonatal vitamin A supplementation on mortality.[14,15] The differences in findings between trials conducted in Asia and Africa may also be attributable to variability in the prevalence of HIV, given that vitamin A supplementation has been associated with higher risk of mother-to-child transmission of HIV.[16] Low birthweight or prematurity are also potential effect modifiers, as vitamin A deficiency is more prevalent among these infants, and these infants may benefit from supplementation.[17] Child sex and timing of vaccination have also been hypothesized to modify the effect of vitamin A supplementation on mortality.[18]

We examined the effects of neonatal vitamin A supplementation on the incidence of all-cause and cause-specific infant morbidity as measured by hospitalization and caregiver report of illness in the NEOVITA Tanzania trial.[5] Additionally, we assessed whether the efficacy of neonatal vitamin A supplementation in reducing infant mortality was modified by baseline maternal and infant characteristics.

## Methods

### Study design and population

The data were collected as part of an individually randomized, placebo-controlled trial conducted in Tanzania from

August 2010 through March 2014. Infants were randomized at home or health facility to receive a mega-dose of vitamin A (50 000 IU) or placebo on the day of birth or within 3 days ($n = 31\,999$). Details regarding the randomization, blinding, intervention and follow up are described elsewhere.[5,19] Infants were eligible for randomization if they were able to feed orally, the family intended to stay in the study area for at least 6 months and parents provided informed consent. Follow-up data were collected during home visits 1 and 3 days after supplementation, as well as 1, 3, 6 and 12 months after supplementation. The study protocol was approved by the institutional review boards of the Harvard School of Public Health, Ifakara Health Institute and Medical Research Coordinating Council of Tanzania, and by the WHO Ethical Review Committee. The trial is registered at Australian New Zealand Clinical Trials Registry (ANZCTR) -ACTRN12610000636055.

## Outcome definitions

The primary outcomes of interest included mortality, hospitalization and morbidity between supplementation and 1 year (360 days). We assessed cause-specific hospitalization and symptom-specific morbidity occurring between supplementation and 1 year (360 days). We also present morbidity and mortality outcomes assessed at 6 months (180 days) as secondary endpoints.

## Potential effect modifiers

Potential effect modifiers of the effect of vitamin A on mortality specified a priori in the trial protocol include infant sex (male or female), birthweight ($< 2500$ g and $\geq 2500$ g), received maternal large-dose vitamin A supplementation (yes or no) and socioeconomic status. Two additional maternal characteristics were considered *post hoc* as potential effect modifiers including maternal vitamin A intake classified by the Institute of Medicine (IOM) recommended daily allowance (RDA) [below RDA ($< 700$ μg/day), within RDA (700 to $< 3000$ μg/day) above RDA ($\geq 3000$ μg/day)][20] and maternal HIV status at delivery (positive or negative). Additionally, we combined information from the maternal large-dose vitamin A supplementation data (yes or no) and the maternal vitamin A intake data (below RDA or within RDA) to create 'maternal vitamin A status' categories: (i) High (maternal supplementation + within RDA); (ii) Medium-High (maternal supplementation + below RDA); (iii) Medium-Low (no maternal supplementation + within RDA); and (iv) Low (no maternal supplementation + below RDA).

## Data collection and categorization

Infant death and date of death were ascertained by research staff at home visits. Hospitalization was defined as an inpatient admission to the hospital since the latest home visit, which was transcribed from the child health card or as reported by the mother in the case of missing child health card. Research staff recorded the admission date and reason for hospitalization as either: (i) acute lower respiratory infection or pneumonia; (ii) diarrhoea; (iii) fever or malaria; or (iv) other reason. Data from the first case of hospitalization were used in the analysis. Caregiver report of morbidity was assessed by 1-month caregiver recall at 1, 3, 6 and 12 month home visits. During home visits, research staff asked caregivers if the child had any of the following symptoms in the past month: cough; refusal to eat, drink, or breastfeed; fever; difficulty in breathing; chest retraction; convulsions; vomiting; diarrhoea.

Child sex and birthweight were assessed by a study nurse or dosing supervisor at randomization. Postpartum maternal vitamin A supplementation (yes or no) was assessed by research staff at randomization and again at 1 month postpartum. Maternal education and pregnancy history were assessed by field interviewers during a baseline interview. A wealth index was generated based on household ownership of assets, and households were categorized into wealth quintiles based on this index. For all women enrolled in the trial during the first year of recruitment, maternal dietary intake was assessed around the time of birth by trained field interviewing using a semi-quantitative food frequency questionnaire (FFQ).[21–25] Based on monthly recall of 108 commonly consumed foods, we calculated average daily servings and translated these data into nutrient intake based on the Tanzania Food Composition Tables.[26] Maternal HIV status (positive, negative, unknown) was abstracted from the delivery ward record books for the subset of women who delivered at health facilities which maintained registry books where HIV status at delivery was recorded. The time of breastfeeding initiation and whether colostrum was given to the infant was assessed by a study nurse or dosing supervisor at the time of dosing and again at 1 and 3 days after dosing if the infant had not initiated breastfeeding at the time of dosing. The age of the child at dosing was calculated as the number of hours between the time of birth and time of dosing. Gestational age at birth was calculated based on maternal report of last menstrual period. Size for gestational age at birth was calculated based on INTERGROWTH standard.[27] Gestational age and size for gestational age was categorized in the following four groups: preterm ($< 37$ weeks of gestation) small for gestations age ($< 10$th percentile in weight for gestational age); preterm

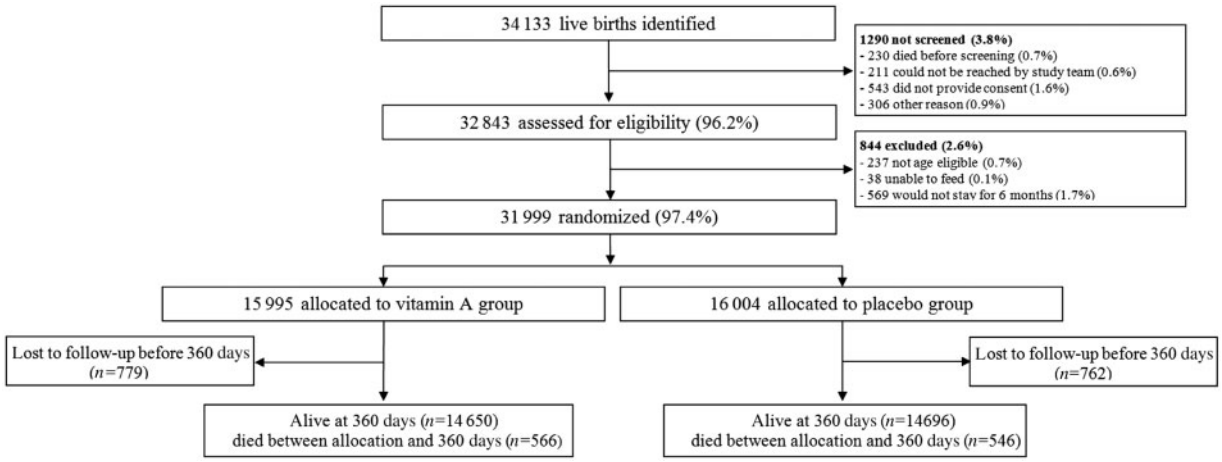


**Figure 1.** Trial profile.

appropriate for gestational age (≥ 10th percentile in weight for gestational age); term (≥ 37 weeks) small for gestational age; or term appropriate for gestational age.

### Statistical analysis

The cohort was characterized using baseline data regarding household, maternal and infant characteristics using means or proportions for continuous and categorical data, respectively. Including all live births, we estimated risk ratios and their corresponding 95% confidence intervals to assess the relationship between vitamin A supplementation and the risks of mortality and hospitalization within 12 months. We used log binomial general estimating equations (GEEs) with an exchangeable working covariance matrix to assess the relationship between vitamin A supplementation and morbidity within 12 months, allowing for repeated episodes of morbidity for each child. For the subgroup analyses, potential effect modification by maternal and infant characteristics (including infant sex, birthweight, maternal vitamin A supplementation, maternal HIV status and maternal vitamin A intake) was assessed using the likelihood ratio test comparing the full and reduced log binomial regression models. We also present mortality, hospitalization and morbidity analyses within the first 6 months (180 days) as secondary analyses. *P*-values less than 0.05, in conjunction with 95% confidence intervals and the magnitude of effect estimates, were used to identify results of importance. Analysis was completed using SAS version 9.2 (Cary, NC).

## Results

Among 32 843 infants assessed for eligibility, a total of 31 999 infants were enrolled in the study between August 2010 and March 2013. Among those enrolled, 15 995 were randomized to the vitamin A group and 16 004 were randomized to the placebo group (Figure 1). Between supplementation and 1 year (360 days), 779 (4.9%) infants were lost to follow-up in the vitamin A group and 762 (4.8%) infants were lost to follow-up in the placebo group.

The mean age at supplementation was 15.5 [standard deviation (SD) 12] h in the vitamin A group and 15.4 (SD 12) in the placebo group; about 80% of infants were supplemented within 24 h after birth. Mean birthweight was 3.02 (SD 1) kilograms in both groups. More than 75% of all women received a mega-dose of vitamin A after delivery (as part of standard care in Tanzania), and the median value of dietary intake of vitamin A for mothers was 940 μg/day [interquartile range (IQR) 574-1389]. Treatment groups were well balanced in regards to demographic, maternal and infant characteristics (Table 1).

At 12 months, vitamin A did not reduce all-cause infant mortality. There were 566 (3.5%) deaths in the vitamin A group and 546 (3.4%) deaths in the placebo group (RR 1.04; 95% CI 0.92-1.16). NVAS did not reduce all-cause hospitalizations or morbidity. There were 596 (3.7%) hospitalizations in the vitamin A group and 547 (3.4%) hospitalizations in the placebo group (RR 1.09; 95% CI 0.97-1.22). NVAS did not affect the incidence of common childhood illnesses through 12 months, with a similar number of caregiver-reported morbidity events in both groups (RR 1.00; 95% CI 0.96-1.05) (Table 2). Similar results were observed in secondary analyses of mortality, hospitalization, and morbidity within six months of age (Supplementary Table A, available as Supplementary data at *IJE* online).

All potential effect modifiers were assessed, and mortality at 12 months did not differ by any characteristic (including sex, birthweight, maternal HIV status, maternal

**Table 1.** Baseline demographic and health characteristics of mothers and infants (n = 31999)

| | Vitamin A Group ($n = 15995$) *n* (%) | Placebo Group ($n = 16004$) *n* (%) |
|---|---|---|
| **Male sex** | 8443 (52.8) | 8340 (52.1) |
| **Birthweight < 2500 grams** | 1908 (11.9) | 1974 (12.3) |
| **Maternal education**[1] | | |
| None | 1335 (9.0) | 1310 (8.8) |
| Primary | 11988 (80.9) | 12066 (81.3) |
| Secondary | 1491 (10.1) | 1472 (9.9) |
| **Received maternal vitamin A supplementation** | 12122 (76.8) | 12091 (76.6) |
| **Colostrum given to infant** | 15390 (97.4) | 15416 (97.6) |
| **Parity**[1] | | |
| 1 | 3872 (29.5) | 3843 (29.2) |
| 2-3 | 5785 (44.1) | 5745 (43.7) |
| ≥4 | 3455 (26.3) | 3551 (27.0) |
| **Time of dosing**[1] | | |
| <24 hours | 12774 (79.9) | 12824 (80.1) |
| 24-47 hours | 2939 (18.4) | 2881 (18.0) |
| ≥ 48 hours | 282 (1.8) | 299 (1.9) |
| **Gestational age & size for gestational age**[1] | | |
| Term AGA | 6768 (66.4) | 6738 (65.8) |
| Term SGA | 1705 (16.7) | 1688 (16.5) |
| Preterm AGA | 1670 (16.4) | 1771 (17.3) |
| Preterm SGA | 46 (0.5) | 46 (0.4) |
| **Initiation of breastfeeding**[1] | | |
| <1 hour | 14083 (88.3) | 14169 (88.9) |
| 2-23 hours | 1726 (10.8) | 1670 (10.5) |
| ≥24 hours | 138 (0.9) | 105 (0.7) |
| **Maternal HIV status** | | |
| HIV infected | 139 (0.9) | 155 (1.0) |
| HIV uninfected | 2747 (17.2) | 2708 (16.9) |
| Not assessed | 13109 (82.0) | 13141 (82.1) |
| **Maternal vitamin A dietary intake** | | |
| <700 μg/day | 1018 (6.4) | 1007 (6.3) |
| 700 to < 3000 μg/day | 1950 (12.2) | 1969 (12.3) |
| ≥3000 μg/day | 28 (0.2) | 32 (0.2) |
| Not assessed | 12999 (81.3) | 12996 (81.2) |

[1]These numbers do not add to 100% due to missing data
AGA, appropriate for gestational age; SGA, small for gestational age.

vitamin A dietary intake or socioeconomic status (data not shown)), except by postpartum maternal vitamin A supplementation (Table 3). The relative risk of mortality from supplementation to 12 months comparing NVAS with placebo for those whose mothers received a large dose of vitamin A was 1.12 (95% CI 0.98-1.29), whereas the relative risk for those infants whose mother did not receive postpartum vitamin A supplementation was 0.86 (95% CI 0.70-1.06) (*P*-value, test for interaction = 0.04). A similar trend was observed by overall maternal vitamin A intake (postpartum vitamin A supplementation and dietary intake). Among children born to mothers with high overall vitamin A dietary intake [who received a postpartum vitamin A supplement and had vitamin A dietary intake within the recommended daily allowance (RDA) according to their food frequency questionnaire], NVAS was associated with an increased risk of infant mortality (RR 1.33; 95% CI 0.88-2.00). Children born to women with the lowest maternal vitamin A status (no maternal supplementation and vitamin A intake below the RDA according to their food frequency questionnaire) had a 40% reduced risk of death associated with NVAS (RR 0.60; 95% CI: 0.26-1.40) (Table 4). Including maternal vitamin A status as an ordinal covariate in the model resulted in a *P*-value for the test for trend of 0.04 and a *P*-value for the test of interaction of 0.07. Qualitatively similar results were observed for effect modification by maternal supplementation and overall vitamin A dietary intake in secondary analyses restricted to events in the first 6 months of life (Supplementary Table B, Supplementary Table C, available as Supplementary data at *IJE* online).

## Discussion

We found that neonatal vitamin A supplementation did not reduce infant mortality or the incidence of hospitalization. Our findings are in accord with those from a systematic review (conducted before the conclusion of the three recent NVAS trials) that found no evidence of an effect of NVAS on hospitalization (RR: 0.75; 95% CI 0.26-2.16), although the authors noted that the quality of available evidence was low.[28] However, NVAS was associated with an increased risk of hospitalization at 6 months in the companion Neovita trial in Ghana (RR 1.11; 95% CI 1.00-1.22).[6] Similarly, a neonatal vitamin A supplementation trial in south India, as well as a trial among older children in Indonesia, found an increased incidence of acute respiratory infection among children supplemented with vitamin A (VA).[29,30] Additionally, research among children hospitalized for acute respiratory infection (ARI) found that vitamin A supplementation increased the severity of symptoms.[31–33] Increased severity of illness is hypothesized to be the result of the pro-inflammatory immune responses associated with VA.[34] We did not find any evidence of effect modification of the effect of neonatal vitamin A supplementation on mortality at 6 or 12 months by child sex. This is consistent with a meta-analysis completed before completion of the three recent NEOVITA trials.[35]

We found there was no difference in the incidence of common childhood morbidities at 6 or 12 months when comparing infants randomized to receive vitamin A at birth and those who were not. Our results regarding hospitalization and morbidity are contrary to the hypothesis

**Table 2.** The effect of neonatal vitamin A supplementation on infant mortality, hospitalization, and morbidity at 12 months

| | Vitamin A | | Placebo | | Risk Ratio[1] (95% CI) | *P*-value |
|---|---|---|---|---|---|---|
| | $n^2$ | $N^2$ | $n^2$ | $N^2$ | | |
| Mortality (All-Cause) | 566 | 15995 | 546 | 16004 | 1.04 (0.92,1.16) | 0.54 |
| Hospitalization (All-Cause) | 596 | 15995 | 547 | 16004 | 1.09 (0.97,1.22) | 0.14 |
| ALRI | 215 | 15995 | 197 | 16004 | 1.09 (0.90,1.32) | 0.37 |
| Diarrhoea | 142 | 15995 | 127 | 16004 | 1.12 (0.88,1.42) | 0.36 |
| Fever | 360 | 15995 | 325 | 16004 | 1.11 (0.96,1.29) | 0.17 |
| Other | 136 | 15995 | 122 | 16004 | 1.12 (0.87,1.42) | 0.38 |
| Morbidity (All-Cause) | 4129 | 38880 | 4125 | 38962 | 1.00 (0.96,1.05) | 0.88 |
| Diarrhoea | 1006 | 38880 | 1016 | 38962 | 0.99 (0.91,1.09) | 0.86 |
| Diarrhoea & Vomiting | 578 | 38880 | 557 | 38962 | 1.04 (0.92,1.18) | 0.53 |
| Diarrhoea & Vomiting & Fever | 518 | 38880 | 502 | 38962 | 1.03 (0.91,1.18) | 0.61 |
| Diarrhoea & Refused Feeding | 449 | 38880 | 441 | 38962 | 1.02 (0.89,1.18) | 0.77 |
| Fever | 2543 | 38880 | 2521 | 38962 | 1.01 (0.96,1.07) | 0.69 |
| Fever & Cough | 1008 | 38880 | 1036 | 38962 | 0.98 (0.89,1.07) | 0.59 |
| Fever & Difficulty Breathing | 583 | 38880 | 552 | 38962 | 1.06 (0.93,1.20) | 0.38 |
| Fever & Cough & Difficulty Breathing | 505 | 38880 | 469 | 38962 | 1.08 (0.94,1.23) | 0.28 |
| Cough | 2125 | 38880 | 2159 | 38962 | 0.99 (0.93,1.05) | 0.68 |

[1]Risk ratio for morbidity outcomes were estimated by GEE log binomial model with an exchangeable working covariance matrix.

[2]*n* is the number of events (*i.e.* deaths, hospitalizations, morbidity cases). *N* is the number of infants for mortality and hospitalization analysis. *N* is the number of household visits for morbidity analysis.

**Table 3.** The effect of neonatal vitamin A supplementation on infant mortality (0-12 months), stratified by subgroup. (n = 31999)

| | Number of newborns supplemented | | | | Risk Ratio (95% CI) | *P*-value | *P*-value test for interaction |
|---|---|---|---|---|---|---|---|
| | Vitamin A | | Placebo | | | | |
| | $n^1$ | $N^1$ | $n^1$ | $N^1$ | | | |
| **Overall** [N = 31,999] | 566 | 15995 | 546 | 16004 | 1.04 (0.92,1.16) | 0.54 | |
| **Sex** [N = 31,994] | | | | | | | |
| Male | 312 | 8443 | 324 | 8340 | 0.95 (0.82,1.11) | 0.52 | 0.09 |
| Female | 254 | 7549 | 222 | 7662 | 1.16 (0.97,1.39) | 0.10 | |
| **Birthweight** [N = 31,983] | | | | | | | |
| <2500 grams | 138 | 1908 | 120 | 1974 | 1.19 (0.94,1.51) | 0.15 | 0.21 |
| ≥2500 grams | 428 | 14077 | 426 | 14024 | 1.00 (0.88,1.14) | 0.99 | |
| **Maternal Vitamin A Supplementation** [N = 31,559] | | | | | | | |
| Yes | 408 | 12122 | 362 | 12091 | 1.12 (0.98,1.29) | 0.10 | 0.04 |
| No | 152 | 3662 | 178 | 3684 | 0.86 (0.70,1.06) | 0.16 | |
| **Maternal HIV Status** [N = 5,749] | | | | | | | |
| HIV infected | 15 | 139 | 10 | 155 | 1.67 (0.78,3.60) | 0.18 | 0.31 |
| HIV uninfected | 65 | 2747 | 59 | 2708 | 1.09 (0.77,1.54) | 0.64 | |
| **Maternal Vitamin A Dietary Intake** [N = 6,004] | 1 | | | | | | |
| <700 μg/day | 36 | 1018 | 41 | 1007 | 0.87 (0.56,1.35) | 0.53 | 0.15 |
| 700 to < 3000 μg/day | 75 | 1950 | 65 | 1969 | 1.17 (0.84,1.61) | 0.36 | |
| ≥3000 μg/day | 0 | 28 | 2 | 32 | – | | |

[1]*n* is the number of deaths. *N* is the number of infants

that vitamin A supplementation affects mortality by reducing the incidence or severity of infant morbidity.[30,36,37] This hypothesis was biologically plausible, as vitamin A is known to play an important role in immune function.[34] Human and animal models illustrate that vitamin A helps maintain and improve epithelial integrity (including in the respiratory and gastrointestinal tracts) and may down-regulate production of pro-inflammatory cytokines in response to specific pathogens. Furthermore, observational data have shown maternal vitamin A deficiency (VAD) is

**Table 4.** The effect of neonatal vitamin A supplementation on infant mortality (0 to 12 months), stratified by maternal vitamin A supplementation and maternal vitamin A dietary intake. (n = 5820)

| | | Number of newborns | | | | Risk Ratio (95% CI) | *P*-value test for trend | *P*-value test for interaction |
|---|---|---|---|---|---|---|---|---|
| | | Vitamin A | | Placebo | | | | |
| | | $n^1$ | $N^1$ | $n^1$ | $N^1$ | | | |
| **Overall** | | 109 | 2911 | 106 | 2909 | 1.02 (0.79,1.34) | 0.84 | |
| **Maternal vitamin A supplementation & dietary intake[2]** | | | | | | | | |
| High | Maternal supplementation + adequate VA dietary intake | 52 | 1418 | 39 | 1415 | 1.33 (0.88-2.00) | 0.04 | 0.07 |
| | Maternal supplementation + inadequate VA dietary intake | 27 | 750 | 27 | 720 | 0.96 (0.57-1.62) | | |
| | No maternal supplementation + adequate VA dietary intake | 22 | 487 | 26 | 506 | 0.88 (0.51-1.53) | | |
| Low | No maternal supplementation + inadequate VA dietary intake | 8 | 256 | 14 | 268 | 0.60 (0.26-1.40) | | |

[1] *n* is the number of deaths. *N* is the number of infants

[2] Vitamin A (VA). Inadequate VA dietary intake is defined as < 700 μg/day. Adequate VA dietary intake is defined as 700 to < 3000 μg/day.

associated with increased morbidity in children. For example, maternal night blindness during pregnancy was associated with an increased risk of diarrhoea, dysentery and acute respiratory infections between birth and 6 months of age among a cohort of infants in South India.[38] Other observational research confirms that VAD children are more likely to be carriers of *Streptococcus pneumoniae* (*Spn*)[39–41] (an important cause of ARI) and have increased rates of ARI morbidity and mortality.[42,43] However, randomized trials in Bangladesh and south India found no difference between the vitamin A and placebo groups in the proportion of infants carrying *Spn* at 3 and 4 months, respectively.[44,45] Our results are consistent with a meta-analysis including neonatal vitamin A supplementation and maternal vitamin A supplementation (MVAS) plus NVAS trials, which found no effect on morbidity between supplementation and 6 months.[46] Similar morbidity results have been documented among trials assessing the efficacy of vitamin A supplementation among children aged 6 to 56 months.[29,36,47,48]

We found evidence that maternal vitamin A status may modify the effect of neonatal vitamin A supplementation. In this trial, NVAS appeared to be beneficial for infants born to mothers who were not supplemented with vitamin A, whereas infants born to women who received postpartum vitamin A supplementation demonstrated a higher risk of mortality associated with neonatal vitamin A supplementation. This finding is consistent with the hypothesis that the prevalence of vitamin A deficiency is an important source of heterogeneity among the recent NVAS trials.[7] The NEOVITA trials in Ghana and Tanzania both suggested the possibility of an increased risk of mortality associated with NVAS, and the prevalence of vitamin A deficiency (< 0.70 μmol/l serum retinol A) among a subset of mothers enrolled in the trials was low in both settings (Ghana: < 3% VAD;[6] Tanzania: 8% VAD[5]). Additionally, the prevalence of postpartum vitamin A supplementation was high in both settings (Ghana: 50% supplemented; Tanzania: 76% supplemented). In contrast, about 12% of women in the companion trial in India trial were vitamin A deficient and no mothers received postpartum vitamin A supplementation; in this context, NVAS was associated with a reduced risk of mortality from supplementation to 6 months.[3] A factorial designed trial of maternal and neonatal vitamin A supplementation trial was conducted in Bangladesh and found no interaction between maternal and neonatal vitamin A supplementation, although the statistical power to detect a moderate or small degree of interaction was limited.[8] Similarly, a factorial designed trial in Zimbabwe found no interaction between maternal and neonatal vitamin A supplementation in an analysis of HIV-uninfected mothers.[13] Notably, as of 2011 the World Health Organization no longer recommends maternal postpartum vitamin A supplementation.[49]

We did not find clear evidence that maternal HIV status modified the effect of neonatal vitamin A supplementation. However, there was a trend showing increased risk of mortality associated with NVAS among infants born to HIV-infected mothers. HIV-exposed neonates supplemented with vitamin A were two times more likely than those in the placebo group to die before 6 months, and they had a 67% increased risk of death by 1 year. Although our cohort for this subgroup analysis was small, our trial is one of two NVAS trials in which the HIV status of mothers

was known. In a trial conducted in Zimbabwe among HIV-infected women which randomized woman and infant pairs to: (i) postpartum maternal vitamin A supplementation (MVAS) alone; (ii) NVAS alone; (iii) both MVAS and NVAS; or (iv) placebo, the unadjusted hazard ratio for child mortality from enrolment to 24 months, comparing neonatal vitamin A supplementation (without maternal vitamin A supplementation) with placebo, was 1.21 (95% CI 0.99-1.46; *P*-value = 0.05).[15] Using fixed-effects meta-analysis, the pooled effect size comparing NVAS with placebo, among infants born to HIV-infected women in the Tanzania and Zimbabwe trials, is 1.23 (95% CI 1.02-1.49) (Supplementary Figure A, available as Supplementary data at *IJE* online). This suggests that NVAS may be harmful for children born to HIV-infected mothers. In the Zimbabwe trial, there was an increased risk of mother-to-child transmission of HIV among the NVAS group, compared with placebo.[15] Similarly, a randomized trial conducted among HIV-infected mothers in Tanzania found that vitamin A was associated with a higher risk of mother-to-child transmission of HIV.[16] As a result, increased mother-to-child transmission may partially explain why we found a trend of increased risk of death associated with neonatal vitamin A supplementation among infants born to HIV-infected mothers.

There are several strengths of this study. First, this is the largest randomized trial of neonatal vitamin A supplementation in sub-Saharan Africa. Detailed baseline data were collected for all mothers and infants, comprehensive longitudinal data about infant illness were collected and loss to follow-up was less than 5% at 1 year. Furthermore, hospitalizations were assessed from the child medical card throughout the course of infancy, thus providing a high-quality measure of severe morbidity. Finally, these data provide perhaps the only opportunity to look at maternal HIV status as a modifier of the effect of neonatal vitamin A supplementation, as additional trials of NVAS among children born to HIV-infected mothers are unlikely.

One limitation of this research is that we used caregiver recall to assess morbidity. Further, mothers were asked to report morbidity within the past 30 days at 1, 3, 6 and 12 months and, as a result, there are no caregiver reports of morbidity for more than half of infancy. Thus, the data reported here are likely an underestimate of the true incidence of infant morbidities. Nevertheless, the analytical methods we used are well suited for data collected by an unbalanced visit schedule. Finally, although this is a large randomized trial, we may lack statistical power to detect moderate to small degrees of interaction in all subgroups. Further, maternal vitamin A dietary intake and HIV status data were collected in only a subset of women enrolled in the trial. Our finding of effect modification by maternal vitamin A status may have occurred by chance, and it is important these results are replicated in other trials.

Overall, our findings are consistent with the hypothesis that NVAS does not affect the risk of infant mortality or the incidence of common childhood morbidities. Furthermore, this study generates additional hypotheses about the potential sources of heterogeneity of the effect of neonatal vitamin A supplementation on infant health, which should be further examined in a pooled analysis of all NVAS trials.

## Supplementary Data

Supplementary data are available at *IJE* online.

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## Author contributions

Designed research (project concept, development of overall research plan and study oversight): E.S., A.M., H.M., W.F. Conducted research (hands-on conduct of the experiments and data collection): E.S., A.M., S.M., C.S., R.N., H.M., W.F. Analysed data or performed statistical analysis: E.S., C.S., D.S. Wrote paper (final paper: only authors who made a major contribution): all authors. Had primary responsibility for final content: E.S., W.F.

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