

Effect of 50 000 IU vitamin A given with BCG vaccine on mortality in infants in Guinea-Bissau: randomised placebo controlled trial

Christine Stabell Benn,¹ Birgitte Rode Diness,¹ Adam Roth,^{1,2} Ernesto Nante,³ Ane Bærent Fisker,³ Ida Maria Lisse,⁴ Maria Yazdanbakhsh,⁵ Hilton Whittle,⁶ Amabelia Rodrigues,³ Peter Aaby³

EDITORIAL by Tielsch

¹Bandim Health Project, Statens Serum Institut, Artillerivej 5, 2300 Copenhagen S, Denmark

²Department of Medical Microbiology, Lund University, 205 02 Malmö, Sweden

³Bandim Health Project, Indepth Network, Apartado 861, Bissau, Guinea-Bissau

⁴Department of Pathology, Herlev University Hospital, 2730 Herlev, Denmark

⁵Department of Immunoparasitology, Leiden University Medical Centre, Leiden 2333 AZ, Netherlands

⁶MRC Laboratories, Fajara, POB 273, Gambia

Correspondence to: C S Benn
cb@ssi.dk

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ABSTRACT

Objective To investigate the effect of high dose vitamin A supplementation given with BCG vaccine at birth in an African setting with high infant mortality.

Design Randomised placebo controlled trial.

Setting Bandim Health Project's demographic surveillance system in Guinea-Bissau, covering approximately 90 000 inhabitants.

Participants 4345 infants due to receive BCG.

Intervention Infants were randomised to 50 000 IU vitamin A or placebo and followed until age 12 months.

Main outcome measure Mortality rate ratios.

Results 174 children died during follow-up (mortality=47/1000 person-years). Vitamin A supplementation was not significantly associated with mortality; the mortality rate ratio was 1.07 (95% confidence interval 0.79 to 1.44). The effect was 1.00 (0.65 to 1.56) during the first four months and 1.13 (0.75 to 1.68) from 4 to 12 months of age. The mortality rate ratio in boys was 0.84 (0.55 to 1.27) compared with 1.39 (0.90 to 2.14) in girls (P for interaction=0.10). An explorative analysis revealed a strong interaction between vitamin A and season of administration.

Conclusions Vitamin A supplementation given with BCG vaccine at birth had no significant benefit in this African setting. Although little doubt exists that vitamin A supplementation reduces mortality in older children, a global recommendation of supplementation for all newborn infants may not contribute to better survival.

Registration Clinical trials NCT00168597.

INTRODUCTION

High dose vitamin A supplementation in children aged above 6 months is associated with significant reductions in overall mortality.¹ In contrast, vitamin A supplementation between 1 month and 5 months of age has not been associated with beneficial effects on mortality.² Two trials from Indonesia and India had both found a significantly beneficial effect of vitamin A supplementation at birth; the reduction in mortality was 64% in Indonesia and 21% in India.^{3,4} In both trials the effect was strongest for boys, with a significant 85% reduction in mortality for boys and only a non-

significant 16% reduction for girls in Indonesia and a significant 30% reduction in boys compared with a non-significant 13% reduction in girls in India. Both studies saw the beneficial effect during the first three to four months of life.^{3,4}

Because of the intriguing age pattern of the effect of vitamin A supplementation on mortality, we hypothesised that vitamin A supplementation interacted with routine childhood vaccinations and was beneficial when given with the live BCG vaccine at birth or live measles vaccine at 6-9 months of age but not when given with inactivated diphtheria-tetanus-pertussis vaccine at 1-5 months of age.² We aimed to investigate the effect of high dose vitamin A supplementation given with BCG vaccine at birth in an African setting with high infant mortality. The primary study hypothesis was that vitamin A supplementation would be associated with at least a 30% reduction in mortality during the first year of life.

METHODS

Setting

The Bandim Health Project has a demographic surveillance system in six suburban districts of the capital of Guinea-Bissau and covers approximately 90 000 inhabitants. All houses in the study area are visited monthly to register new pregnancies and births. Once a newborn infant is identified, the child is followed with home visits every third month.

Guinea-Bissau provides BCG and oral polio vaccine at birth, combined diphtheria-tetanus-pertussis and oral polio vaccine at 6, 10, and 14 weeks of age, and measles vaccine at 9 months of age. The World Health Organization's recommendations for vitamin A supplementation after 6 months of age are not implemented in Guinea-Bissau. Guinea-Bissau is classified by Unicef as having subclinical vitamin A deficiency.⁵

Participants

The trial took place between 13 November 2002 and 28 November 2004. We invited mothers who gave birth at the maternity wards of the national hospital and a local health centre to participate in the study. We invited

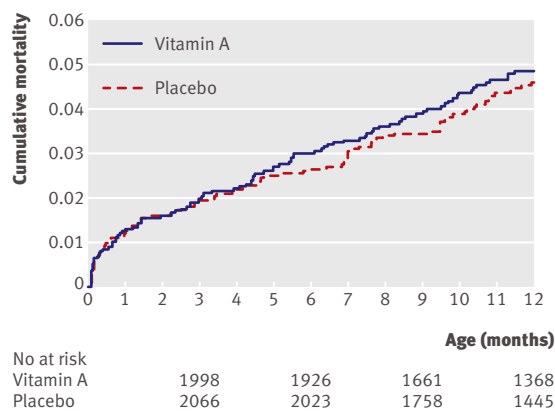


Fig 1 | Kaplan-Meier estimates of death in vitamin A and placebo recipients

mothers who delivered at home to participate when they came for BCG vaccination. The inclusion criteria were weight at least 2500 g at presentation and no signs of overt illness or malformations.

Blinding

The vitamin A and placebo bottles looked alike. None of the three assistants who were responsible for the randomisation procedures had any idea which bottles contained vitamin A and which placebo. The assistants who later followed the children were also unaware of treatment allocation.

Outcomes examined in the trial

We followed more than 2000 of the children for adverse events and immune response to BCG during the first months after supplementation with 50 000 IU vitamin A or placebo.⁶⁷ We concluded that vitamin A supplementation with BCG vaccination was not associated with serious adverse events and did not seem to interfere with the long term immune response to BCG.⁶⁷

For all children, deaths were registered at each routine home visit and at a special follow-up visit at age 12 months. Deaths were followed by a verbal autopsy by a trained local physician. A panel of three medical doctors reached consensus on the cause of death.

Statistical analysis

We assessed survival in Cox proportional hazards models. Infants provided person years at risk from enrolment until they reached 12 months of age, moved, died, or received vitamin A supplementation in a campaign. Our intention was to study the effect of vitamin A supplementation on overall mortality. Accumulating evidence for sex differential effects of vitamin A supplementation made us hypothesise that supplementation would be particularly beneficial for boys.⁸⁻¹⁰ We did explorative analyses to study whether baseline characteristics and season could have modified the response to vitamin A supplementation. We analysed effect modification by investigating the homogeneity of the effect of vitamin A

supplementation in the different categories of the suspected modifier.

RESULTS

Participant flow and baseline data

We enrolled 4345 children, of whom 174 died within the first year of life—a mortality rate of 47/1000 person years. Seventy children were lost to follow-up. A total of 1181 children were enrolled after the first week of life. The effect of vitamin A supplementation did not differ with age of supplementation ($P=0.95$). No differences in baseline characteristics existed between the two intervention groups.

Outcomes and estimation

Vitamin A supplementation was not significantly associated with survival during the first year of life; the overall mortality rate ratio was 1.07 (95% confidence interval 0.79 to 1.44; $P=0.66$ for effect of vitamin A supplementation) (fig 1). The age at vaccination did not matter for the estimated effect of vitamin A supplementation (data available on request). Mortality within the first 7 days of life was high; 20 (mortality 349/1000 person years) of the children died during this period—10 vitamin A and 10 placebo, mostly from septicaemia/asphyxia ($n=13$) or acute haemorrhage ($n=4$). Excluding the 20 perinatal deaths resulted in an overall effect of vitamin A supplementation of 1.08 (0.79 to 1.48). The previous studies saw a beneficial effect only during the first four months of life.³⁴ We found the mortality rate ratio to be 1.00 (0.65 to 1.56) during this period (79 deaths) and 1.13 (0.75 to 1.68) from 4 to 12 months of age (95 deaths).

Sex

We found a tendency for a sex differential effect of vitamin A supplementation; the mortality rate ratio in boys was 0.84 (0.55 to 1.27) compared with 1.39 (0.90 to 2.14) in girls (P for interaction=0.10) (fig 2). The differential effect was not apparent before 4 months of age (boys 0.94 (0.52 to 1.71), girls 1.09 (0.56 to 2.11); P for interaction=0.76) but was marked in the period from 4 to 12 months of age (0.74 (0.41 to 1.34) versus 1.67 (0.94 to 2.97); P for interaction=0.05).

Explorative analyses

Stratified analyses according to mother/child characteristics

We looked for any differential effect of vitamin A stratified according to characteristics of mothers or children that might be associated with vitamin A status. Overall, the effect of vitamin A supplementation on mortality did not differ by maternal education, maternal arm circumference, or children's anthropometrics at enrolment.

Season

We found a strong interaction between vitamin A and season of distribution. Vitamin A supplementation administered in the dry season was associated with a mortality rate ratio of 0.63 (0.41 to 0.97), whereas

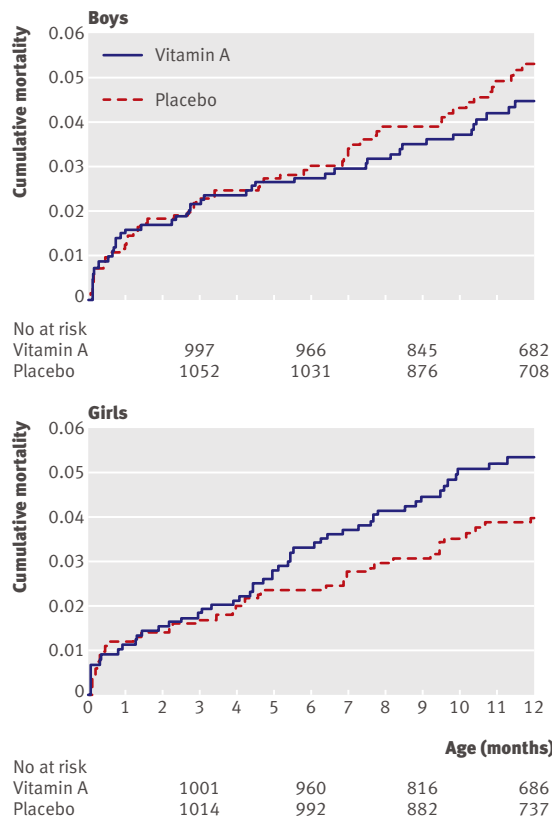


Fig 2 | Kaplan-Meier estimates of death in vitamin A and placebo recipients by sex

vitamin A supplementation administered in the rainy season was associated with a mortality rate ratio of 1.84 (1.19 to 2.85). The negative effect of receiving supplement in the rainy season was evident in boys as well as girls. As a consequence, vitamin A was associated with a significantly increased mortality in girls supplemented in the rainy season (mortality rate ratio 2.23 (1.18 to 4.24); $P=0.01$) but a significantly beneficial effect among boys supplemented in the dry season (0.45 (0.24 to 0.84); $P=0.01$).

Causes of death

Main causes of death were septicaemia, malaria, diarrhoea, and respiratory infections. The negative effect of vitamin A supplementation administered in the rainy season was apparent for deaths from malaria, diarrhoea, and respiratory infections but not for deaths from septicaemia. The sex differential effect was most apparent for diarrhoea; vitamin A supplementation was associated with significantly more deaths from diarrhoea among girls, particularly if they received supplement in the rainy season.

DISCUSSION

Principal findings

We were unable to show an important effect of vitamin A supplementation on overall mortality, but the effect of supplementation tended to be beneficial for boys but harmful for girls. We saw a strong interaction between vitamin A supplementation and season; vitamin A

supplementation was beneficial when provided in the dry season but detrimental when provided in the rainy season.

Strengths and weaknesses

Strengths of the study include the demographic surveillance system that allowed us, in an African setting, to keep track of a very large percentage of the children enrolled at the hospital and at the health centres. All eligible children were enrolled in the study. Interviews with mothers and assistants indicated that the blinding was successful.

Limitations include the fact that the mortality was much lower (47/1000 person years) than anticipated (70/1000 person years), probably in part because we offered free consultations and essential drugs during the first year of life for eligible children. This decreased our power to estimate the effect of vitamin A supplementation, and the confidence interval of the overall estimate still leaves room for clinically important effects.

Possible explanations of contrasting results

When we started our trial, two similar trials from Asia had reported beneficial effects of vitamin A supplementation at birth.^{3,4} While our trial was ongoing, a trial from Zimbabwe supplementing women and their offspring could not reproduce a beneficial effect of vitamin A supplementation at birth. The Zimbabwe trial was done in an area that is not endemic for malaria, and this was speculated to be the reason for the apparent lack of a beneficial effect. However, we found no effect of vitamin A supplementation against deaths from malaria.

The conflicting results could be due to an underlying difference in degree of vitamin A deficiency. As the direct measures of vitamin A status varied between the studies, no firm conclusions can be reached, however, inspection of data shows nothing that indicates that differences in vitamin A status alone can account for the apparent beneficial effect in Indonesia and India but not in Zimbabwe or Guinea-Bissau.

Similarly, maternal education is an important socio-economic indicator, and vitamin A status may differ by maternal education.¹¹ In our trial, educated mothers had significantly higher retinol binding protein than mothers with no education.¹² However, the variations in maternal education do not fit with this explanation of the conflicting results.

The percentage of low birthweight children differed considerably between studies. Low birthweight children are at greatest risk of vitamin A deficiency.¹³ However, differences in birth weight do not seem able to explain the differences either.

Sex differences

The two Asian studies reported a more beneficial effect in boys, a finding that we could replicate in our study, although it was not significant at the 5% level. However, unlike the Asian studies we found a tendency for a negative effect in girls. We have previously

WHAT IS ALREADY KNOWN ON THIS TOPIC

Vitamin A supplementation at birth has been associated with decreased mortality in Asia

WHAT THIS STUDY ADDS

No important beneficial effect of vitamin A supplementation was found in an African setting

Vitamin A supplementation may benefit boys more than girls

Vitamin A supplementation interacted strongly with season, being beneficial during the dry season but harmful during the rainy season

reported that boys had a stronger antibody response from measles vaccine administered with vitamin A supplementation,¹⁴ and girls in contrast to boys benefited from receiving lower doses of vitamin A supplementation than the ones currently recommended.⁸ The reason for these differences between the sexes is unknown but potentially very important for designing the optimal vitamin A policy.

Seasonal effects

An explorative analysis revealed a strong interaction with season of supplementation, resulting in a significantly beneficial effect of vitamin A supplementation if given to boys during the dry season but a significantly negative effect if given to girls during the rainy season. Vitamin A supplementation administered in the rainy season tended to be associated with increased mortality from malaria, diarrhoea, and respiratory infections. Several studies have reported that the growth response to vitamin A supplementation depended on season.¹⁵⁻¹⁷ If health interventions such as vitamin A supplementation have differential seasonal effects, this would have major consequences for public health practice in low income countries.

Biological mechanisms

We have no well documented explanation of why vitamin A supplementation should have sex differential and season differential effects. One could speculate that underlying differences in the prevalence of vitamin A deficiency between the sexes and between seasons might explain the results. However, in our population boys were no more vitamin A deficient than girls at 6 weeks, and at 4 months they had higher retinol binding protein concentrations than girls.¹²

In immunological studies, vitamin A has mostly been shown to enhance T helper (Th) 2 type responses.¹⁸ Indications are that boys may have a more pronounced Th1 profile than girls as they have a stronger delayed hypersensitivity response.⁷ Conversely, girls may have a stronger Th2 profile as they usually mount a higher antibody response than boys.¹⁴ We might speculate that the sex differential effect is due to vitamin A supplementation inducing a more balanced and beneficial Th1/Th2 profile in boys but unnecessary or excessive Th2 deviation in girls.

Treatment with vitamin A has been shown to have disease specific effects.¹⁸ The seasonal differences could be due to seasonal differences in the prevalence of certain disease types against which vitamin A supplementation is particularly beneficial or harmful.

Overall evidence

We did this study believing that vitamin A supplementation would contribute to further reductions in mortality in our African setting. This did not happen. Vitamin A supplementation may indeed have a beneficial effect in some situations. However, it apparently also interacted with other, as yet unknown, environmental factors to produce a negative effect on survival in some situations.

On the basis of previous studies, recommendation of neonatal vitamin A supplementation at birth in Asia, but not in Africa, has recently been suggested.^{19,20} However, before moving to policy we need to resolve the contradictions to identify the situations in which vitamin A supplementation is beneficial or harmful and to clarify the underlying mechanisms. Given the current evidence, a global or regional recommendation of 50 000 IU vitamin A supplementation at birth is unwarranted.

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Case-control study of self reported genitourinary infections and risk of gastroschisis: findings from the national birth defects prevention study, 1997-2003

Marcia L Feldkamp,^{1,2} Jennita Reefhuis,³ James Kucik,³ Sergey Krikov,^{1,2} Andy Wilson,^{1,2} Cynthia A Moore,³ John C Carey,^{1,2} Lorenzo D Botto^{1,2}

EDITORIAL by Mastroiacovo

¹Division of Medical Genetics, Department of Pediatrics, University of Utah Health Sciences Center, Salt Lake City, UT 84132, USA

²Utah Birth Defect Network, Utah Department of Health, Utah

³National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia

Correspondence to: M L Feldkamp marcia.feldkamp@hsc.utah.edu

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ABSTRACT

Objective To assess the association between genitourinary infections in the month before conception to the end of the first trimester and gastroschisis.

Design Case-control study with self reported infections from a computer assisted telephone interview.

Setting National birth defects prevention study, a multisite, population based study including 10 state surveillance systems for birth defects in the United States.

Participants Mothers of 505 offspring with gastroschisis and 4924 healthy liveborn infants as controls.

Main outcome measure Adjusted odds ratios for gastroschisis with 95% confidence intervals.

Results About 16% (n=81) of case mothers and 9% (n=425) of control mothers reported a genitourinary infection in the relevant time period; 4% (n=21) and 2% (n=98) reported a sexually transmitted infection and 13% (n=67) and 7% (n=338) reported a urinary tract infection, respectively. Case mothers aged <25 years reported higher rates of urinary tract infection alone and in combination with a sexually transmitted infection compared with control mothers. In women who reported both types of infection, there was a greater risk of gastroschisis in offspring (adjusted odds ratio 4.0, 95% confidence interval 1.4 to 11.6).

Conclusion There is a significant association between self reported urinary tract infection plus sexually transmitted infection just before conception and in early pregnancy and gastroschisis.

INTRODUCTION

Gastroschisis is a rare congenital malformation that occurs in about 1 in 2700 births. Several studies have tried to identify an environmental risk factor that could account for the rapidly increasing occurrence of

gastroschisis in several countries worldwide,¹⁻⁵ especially in infants of mothers under 20 years compared with mothers aged 25 or older.⁶ Researchers have identified epidemiological associations with smoking, alcohol use, and use of common medications. It is unclear, however, if these findings reflect causal effects or explain the rising rates of gastroschisis.

We examined genitourinary infections as potential risk factors for gastroschisis as they are common among sexually active young women, and the frequent and increasing rates of infections among women make this a reasonable focus of investigation. The investigation was conducted as part of the national birth defects prevention study.^{7,8}

METHODS

Study design

The national birth defects prevention study is a multisite, population based, case-control study of genetic and environmental risk factors for birth defects supported and coordinated by the US Centers for Disease Control and Prevention. Cases are identified through 10 population based surveillance programmes in 10 states, according to mother's residence. Liveborn infants, stillbirths, and terminations of pregnancy are eligible. Concurrently, liveborn infants are selected randomly from the same birth population to serve as controls, without any matching. Details of study methods have been published.⁷ Once enrolled in the study, mothers of affected and control infants take part in a computer assisted telephone interview. During the interview, trained staff systematically collect data on demographics, use of medication, illnesses, occupation, lifestyle, and other exposures from three months before pregnancy

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