

The effect of high-dose vitamin A supplementation at birth on measles incidence during the first 12 months of life in boys and girls: an unplanned study within a randomised trial

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Abstract

Vitamin A treatment reduces mortality during acute measles infection, and vitamin A supplementation (VAS) to children above 6 months of age may reduce the incidence of measles infection. The effect of VAS at birth on measles incidence is unknown. In a randomised placebo-controlled trial in Guinea-Bissau, normal-birth-weight newborns were randomised to 50 000 IU (15 mg) VAS or placebo. During the trial, a measles epidemic occurred. We linked data from the trial with data from the measles infection surveillance and studied the effect of VAS on the measles incidence before 12 months of age in both sexes. A total of 165 measles cases were identified among the 4183 children followed from 28 d of age. Up to 6 months of age, the incidence rate ratio of measles for VAS compared with placebo was 0.54 (95% CI 0.25, 1.15) among boys and 1.57 (95% CI 0.80, 3.08) among girls (test of interaction, $P=0.04$). The corresponding figures at 12 months were 0.67 (95% CI 0.43, 1.05) and 1.17 (95% CI 0.76, 1.79) (test of interaction, $P=0.08$). VAS compared with placebo tended to be associated with less measles hospitalisation or death during the first 6 months of life in boys ($P=0.06$), but not in girls. VAS at birth may affect the susceptibility to measles infection during the first 6 months of life in a sex-differential manner.

Key words: Vitamin A: Sex differences: Measles: Infant mortality

Randomised trials of prophylactic vitamin A supplementation (VAS) to children aged 6 months or older have reported that VAS tended to be associated with lower measles incidence⁽¹⁾ and fewer measles deaths^(2,3). The effect of VAS administered at birth on the incidence and severity of measles infection has not been studied.

From 2002 to 2005, we conducted a randomised trial testing the effect on the mortality and morbidity of 50 000 IU (15 mg) of vitamin A with Bacille Calmette Guérin vaccine at birth in Guinea-Bissau. In 2003–4, a severe measles epidemic leading to many cases of measles occurred. We used the situation to study the effect of VAS at birth on the incidence and severity of measles infection. As previous studies have suggested sex-differential effects of VAS⁽⁴⁾, we conducted the analyses separately for each sex. Since it was unpredictable that a large measles epidemic would occur, the present study was by nature an unplanned study.

The present study has been registered with clinicaltrials.gov (no. NCT00168597).

Materials and methods

The Bandim Health Project (BHP) maintains a demographic surveillance system in six districts of Bissau, Guinea-Bissau. All children below 3 years of age are visited every 3 months.

Recruitment to the randomised VAS-at-birth trial took place from 2002 to 2004 and has been described in detail elsewhere⁽⁵⁾. In brief, all newborns from the study area who weighed ≥ 2500 g, had no overt illness and came to receive Bacille Calmette Guérin vaccine were eligible. A total of 4345 infants were randomised to receive oral vitamin A (50 000 IU (15 mg), 2145 children) or placebo (2200 children). Enrolled children were followed by the demographic surveillance system, and furthermore all were visited at 12 months of age.

The current recommendation in Guinea-Bissau is to provide measles vaccine at 9 months of age. At the time of the VAS trial, the BHP conducted a two-dose measles vaccine trial testing the effect of providing measles vaccine at 4.5 and 9 months of age⁽⁶⁾. Vaccinations at the health centres in the study area are registered daily. Vaccinations elsewhere are

Abbreviations: BHP, Bandim Health Project; IRR, incidence rate ratio; VAS, vitamin A supplementation.

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documented at the regular home visits. Hence, we could censor follow-up for children when they received measles vaccine to assure that we assessed only the effect of VAS on measles infection among measles unvaccinated children.

In November 2003 and November 2004, VAS campaigns provided VAS to children aged 6 months or older. VAS campaigns in the study area are fully documented for individual children. Hence, we could censor follow-up when children received VAS in a campaign to assure that we measured only the impact of VAS at birth on measles infection.

Measles epidemic

From the autumn of 2003 to May 2004, Bissau experienced a large measles epidemic with more than 1700 cases. For many years, the BHP has had a regular surveillance for measles cases based on monthly visits to all houses. This system functioned throughout the epidemic. During the epidemic, suspected measles cases were also detected by surveillance at the local health centres, the paediatric ward at the National Hospital and general surveys to identify new cases. Furthermore, many children were brought to the BHP for treatment⁽⁶⁾.

Laboratory analysis

Whenever possible, two blood samples were collected 4–6 weeks apart from suspected measles cases for serological testing. IgG measles antibody analysis was done by the measles haemagglutination inhibition test⁽⁶⁾. Children for whom it was only possible to obtain one sample were tested by an IgM test. We considered a positive IgM test or a fourfold increase in IgG antibody concentration to be serological confirmation⁽⁶⁾.

Measles diagnosis

Measles diagnoses were made by local physicians. Cases were divided into three categories: (1) serologically confirmed cases; (2) clinical measles cases seen in the acute phase, the diagnosis of measles being based on at least one of the three major symptoms (Koplik's spots, a typical rash or a typical desquamation), as well as the presence of one or more of the other signs characteristic of measles infection including cough, fever, conjunctivitis and stomatitis; (3) retrospective diagnoses made by physician through interview or verbal autopsy. Negative IgG responses in convalescent sera were considered to invalidate a measles diagnosis⁽⁶⁾.

Statistical analysis

Measles incidence was examined in Cox proportional hazards models with age as underlying time, providing incidence rate ratios (IRR). Infants were considered at risk when they were enrolled in the randomised study and the neonatal period was over. We examined the incidence of measles up to 6 and 12 months of age. Children were censored when they moved, died, received VAS in a campaign or received measles

vaccination. Hence, the focus in the present analysis was on the impact of VAS administered at birth on the measles incidence among measles unvaccinated children who did not receive additional VAS at one of the later time points. The risk of mortality and hospitalisation conditional on measles infection was compared between groups in logistic regression models. All analyses were conducted and stratified by sex. Analyses were made using Stata 9.2 (Statacorp LP, College Station, TX, USA).

Ethical approval

The present study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects/patients were approved by the Ministry of Health in Guinea-Bissau and the Danish Central Ethical Committee. Written informed consent was obtained from subjects/patients who knew how to write; for the others, verbal consent was witnessed and formally recorded⁽⁵⁾.

Results

We followed 4183 children from 28 d of age. The baseline characteristics of the two treatment groups were comparable (data not shown). Of the 4183 children, 165 (3.9%) developed measles within the first 12 months of life. Among the 165 cases, seventy-four (45%) had serological confirmation, fifty-nine (36%) had a clinical diagnosis and thirty-two (19%) were reported retrospectively. Based on the serological tests, six suspected cases were refuted.

As shown in Table 1, the measles incidence increased with increasing age, being 4.1/100 person years between 0 and 5 months of age and 11.9/100 person years from 6 to 11 months of age. There was no overall effect of VAS among measles unvaccinated children under 12 months of age, the IRR being 0.89 (95% CI 0.66, 1.21). However, the IRR in boys was 0.67 (95% CI 0.43, 1.05) and 1.17 (95% CI 0.76, 1.79) in girls (*P* for interaction between VAS and sex 0.08) (Table 1). Before 6 months of age, the IRR was 0.97 (95% CI 0.60, 1.58); the IRR was 0.54 (95% CI 0.25, 1.15) in boys and 1.57 (95% CI 0.80, 3.08) in girls. Hence, the effect of VAS was significantly different for boys and girls (*P* for interaction=0.04). Restricting the analyses to the thirty-two serological confirmed measles cases did not change the estimates, the IRR being 0.39 (95% CI 0.13, 1.23) in boys and 1.49 (95% CI 0.57, 3.92) in girls (*P* for interaction 0.08).

Severe measles defined as measles causing hospitalisation or death was observed in forty (24%) of the 165 cases before 12 months of age, including fifteen VAS recipients (nine boys and six girls) and twenty-five placebo recipients (sixteen boys and nine girls) (*P*=0.21). Before 6 months of age, three VAS recipients (zero boys and three girls) and eight placebo recipients (seven boys and one girl) suffered from severe measles (*P*=0.18), suggesting a protective effect of VAS against severe disease in boys (*P*=0.06, Fisher's exact test) but not in girls (Breslow–Day test of homogeneity of effects in boys and girls: *P*=0.08).

Table 1. Effect of vitamin A supplementation (VAS) given with Bacille Calmette Guérin vaccine at birth on measles infection*

Age at risk (months)	Measles incidence rate/100 pyrs	Boys						Girls						Test of interaction between VAS and sex					
		Vitamin A			Placebo			Vitamin A			Placebo								
		Cases	Fatalities	Pyrs	Cases	Fatalities	Pyrs	Cases	Fatalities	Pyrs	Cases	Fatalities	Pyrs		Incidence ratio (vitamin A/ placebo)	95% CI			
1-5	4.1	3.2, 5.2	10	0	390	20	3	419	0.54	0.25, 1.15	21	1	386	14	0	399	1.57	0.80, 3.08	0.04
6-11	11.9	9.1, 13.4	21	2	223	30	3	243	0.76	0.44, 1.33	22	0	205	27	2	236	0.95	0.54, 1.66	0.59
Total	6.6	5.7, 7.7	31	2	613	50	6	662	0.67	0.43, 1.05	43	1	591	41	2	635	1.17	0.76, 1.79	0.08

Pyrs, person years at risk.

* Children censored at 12 months of age, measles vaccination, permanent migration from the study area or additional vitamin A supplementation.

Discussion

As expected, the measles incidence increased with increasing age, and loss of measles-specific maternal antibodies acquired at birth. In contrast to previous reports among older children, we found no overall beneficial effect of VAS at birth on measles infection after either 6 or 12 months of follow-up. However, VAS at birth tended to protect against measles infection and to reduce the severity of infection for boys in the first 6 months of life when one would expect the effect of a neonatal dose to be strongest. In girls, the tendency was opposite, but disappeared when the children were followed to 12 months of age.

The study has apparent weaknesses. It was not a planned study. During the epidemic, the workload was heavy, not all cases could be visited, we did not obtain blood samples from all, and it was only possible to obtain serological confirmation from 45% of the cases. However, since the VAS trial was successfully randomised and blinded⁽⁵⁾, and the investigation of measles infection was carried out by a different team unaware of the allocated treatment⁽⁶⁾, we find it unlikely that differential assessment of measles cases in the randomisation groups could have influenced the results. Trends were the same when the analysis was restricted to serologically confirmed cases. Irrespective of case definition, the number of events was small, and no firm conclusions can be drawn. Nonetheless, we find it interesting that the results supported our hypothesis that VAS at birth would benefit boys more than girls⁽⁴⁾.

There are very limited sex-specific data on the effect of prophylactic VAS on measles incidence and severity. Two meta-analyses of the effect of prophylactic VAS studied the effect on measles-specific mortality and reported relative risks of 0.74 (95% CI 0.53, 1.04) and 0.61 (95% CI 0.32, 1.15), respectively^(2,3). The data were not presented by sex. Within a randomised VAS trial in Ghana, there was no overall effect of VAS on measles incidence and acute measles case fatality. It was noted that the case fatality was somewhat higher in girls than in boys (adjusted OR 1.3, 95% CI 0.9, 2.1)⁽¹⁾. In Cape Town, among hospitalised measles cases, those who received 400 000 IU vitamin A had significantly lower mortality than those who did not, but the female/male mortality ratio increased from 1.65 to 2.0 when VAS was implemented as part of standard measles treatment⁽⁷⁾, suggesting that the beneficial effect was stronger for boys.

The data on mortality support that VAS at birth may have sex-differential effects. Of seven trials of the effect of VAS at birth on mortality, four reported a more beneficial effect in boys, one trial found a slightly better effect for girls whereas two trials did not report data by sex⁽⁸⁾.

A more beneficial effect of VAS at birth among boys could be due to neonatal boys being more vitamin A deficient. However, in a subgroup from the present trial, boys had better vitamin A status than girls at 4 months of age⁽⁹⁾. Almost all children were still being breast-fed at 12 months of age, equally many boys (95%) and girls (95%) (unpublished results), so there is no evidence to suggest that different breast-feeding patterns explain the observed sex differences.

We have previously observed that girls may lose their measles-specific antibodies more rapidly than boys and become susceptible at a younger age⁽¹⁰⁾. It is unknown whether VAS affects maternally acquired antibodies, but if so, sex differences in the persistence of maternal antibodies could potentially help explain the observed sex differences in the effect of VAS on measles incidence. Noteworthy, we have previously reported that boys who received VAS with measles vaccine had a better measles-specific antibody response⁽¹¹⁾. It may be that boys who receive VAS also have a better innate response and therefore less clinical measles infections.

In conclusion, the present study suggests that VAS at birth might be beneficial for boys during measles epidemics. The present results were not statistically significant separately for boys. However, if VAS reduces the incidence of measles by 46% before 6 months of age, this is no small effect. VAS at birth might be considered as a preventive measure in epidemics, refugee camps and other emergency situations with a high degree of crowding and rapid transmission of infections if our findings are confirmed elsewhere. At present, three WHO-sponsored trials studying the effect of VAS at birth on overall mortality are being initiated and may provide an opportunity to test our observations.

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