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The effect of high-dose vitamin A supplementation administered with BCG vaccine at birth may be modified by subsequent DTP vaccination☆

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ABSTRACT

Unexpectedly, we found no overall beneficial effect on mortality in a randomised trial of vitamin A supplementation (VAS) or placebo administered with BCG vaccine at birth in Guinea-Bissau. We conducted an explorative analysis to examine whether subsequent diphtheria–tetanus–pertussis (DTP) vaccinations had modified the effect of VAS at birth. VAS was associated with a weak tendency for decreased mortality as long as BCG was the most recent vaccination, the mortality rate ratio being 0.86 (0.48–1.54); 0.82 (0.32–2.08) in girls and 0.89 (0.43–1.88) in boys. However, after DTP vaccination VAS at birth was associated with increased mortality in girls (2.19 (1.09–4.38)), whereas no difference was seen for boys (0.90 (0.44–1.82)) ($p = 0.08$ for equal effect of VAS in the two sexes if DTP is the last vaccine). The explanation for the lack of beneficial effect in our setting may have been that VAS at birth interacted negatively with subsequent DTP vaccinations in girls.

1. Introduction

Three randomised trials from Asia have reported a beneficial effect on mortality of vitamin A supplementation (VAS) at birth [1–3]. One of the studies followed children to 12 months of age [1]. The beneficial effect was only apparent in the first 4 months of life. The two other studies followed children to 6 months of age [2,3]. The largest effect was observed in the first 3–4 months of life. There was a tendency for a more beneficial effect in boys in two of the studies [1,2], but not in the third study [3]. In contrast, a recent trial from Zimbabwe randomised both mothers and neonates to VAS in a two-by-two factorial design, and found no beneficial effect of VAS at birth on mortality at 12 months of age [4,5]. The survival curves indicated that during the first 2 months of life mortality was highest in the group in which mother as well as child received placebo (Fig. 2 in Ref. [4]). However, after the first months, mortality was higher in the two groups in which the children received VAS and this tendency remained until 12 months of age. The data were not reported by sex [6].

We have conducted a randomised trial of the effect on mortality of 50,000 IU vitamin A administered simultaneously with BCG at birth in Guinea-Bissau. The main results were reported elsewhere [7]. In brief, among 4345 participating infants we found no overall beneficial effect of VAS, the mortality rate ratio being 1.07 (0.79–1.44) [7]. However, the effect of VAS tended to differ between boys and girls, especially after the first months of life. From 4 to 12 months of age; the mortality rate ratio in boys was 0.74 (0.41–1.34) compared with 1.67 (0.94–2.97) in girls (p for equal effect of VAS in the two sexes = 0.05) [7].

The overall results from the three Asian studies and the two African studies are conflicting, since the Asian studies found a beneficial effect of VAS [1–3] whereas the African studies did not [4,5,7]. Nonetheless there are some similarities between the studies. All studies suggest that the effect of VAS at birth is not constant over time. It may be beneficial during the first 2–4 months of life but this effect disappears and may even be counteracted by a negative effect later in infancy. Furthermore, three of the four studies that published results by sex found that VAS tended to benefit boys more than girls [1,2,7].

It would seem important to explain these contrasts and similarities. Understanding the mechanisms might have consequences for how and to whom VAS should be distributed to optimise its beneficial effect on child survival. Particularly, it would seem important to understand the apparent later increase in mortality in the African trials.

☆ *Trial registration*: The study was registered under clinicaltrials.gov, number NCT00168597.

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We have previously proposed the hypothesis that VAS amplifies the non-specific effects of routine childhood vaccines, being beneficial when given in the time-window of the live vaccines such as BCG vaccine (recommended at birth) or measles vaccine (9 months of age), but potentially harmful when given when the inactivated DTP vaccine is the predominant vaccine (1–5 months of age) [8]. Accordingly, we expected VAS given with BCG at birth would be beneficial. However, the contradictory results made us speculate that the potential beneficial effect of VAS with BCG at birth may have been counteracted by a negative interaction between VAS and the subsequent DTP vaccinations.

Hence, within the Guinea-Bissau trial we conducted a post hoc explorative analysis comparing the effect of VAS while BCG was the last vaccine received with the effect of VAS once the children received DTP vaccine. Due to the observed sex-differences in response to VAS [1,2,6,7,9,10], and due to consistent observations of sex-differential non-specific effects of routine vaccinations [11–13], we analysed all data by sex.

2. Methods

2.1. Setting and population

The Bandim Health Project (BHP) has a demographic surveillance system (DSS) in six districts of the capital of Guinea-Bissau, covering approximately 90,000 inhabitants. The study area is poor. Most people live in multi-family mud-brick houses with zinc or straw roofs. More than 60% have no electricity in the house. Around 30% of the mothers in the present trial had no education. All houses in the study area are visited monthly to register new pregnancies and births. Once a newborn is identified, the child is followed with home visits every third month to register vaccinations, infections, hospitalisations, feeding patterns and survival.

2.1.1. VAS campaigns

In recent years, VAS has been provided in yearly campaigns. While this study was conducted, there were two national VAS campaigns in November 2003 and November 2004 during which children between 6 months and 5 years of age were offered VAS. The BHP registered all the children in the study area who received VAS during these campaigns.

2.1.2. Vaccinations

Guinea-Bissau follows the WHO recommendations of providing BCG and oral polio vaccine (OPV) at birth, combined DTP and OPV at 6, 10, and 14 weeks of age, and measles vaccine at 9 months of age (Fig. 1). However, during the conduct of the trial, there were several deviations from the WHO recommendations:

2.1.3. Early measles vaccination trial

From August 2003 and onwards, an early measles vaccination trial was conducted in the study area [14]. During the period, mothers of children between 1½ and 4 months of age were visited and encouraged to get their child DTP vaccinated according to the recommended schedule. All children who had received 3 DTP vaccinations at 4½ months of age were offered participation. Provided maternal consent they were randomised to an early measles vaccine at 4½ months of age (one third) or no such early vaccine (two thirds). All children received a measles vaccine at 9 months of age. By linking the study databases we could identify the children who took part in that study and their exact dates of measles vaccination.

2.1.4. Lack of OPV at birth

During 2004, Guinea-Bissau experienced several periods with lack of OPV. The main periods were from February to May 2004, briefly in June 2004, and from October to November 2004. The BHP registered whether a child got OPV at the same time as BCG [15].

2.2. Procedures

Between November 13, 2002, and November 28, 2004, mothers giving birth at the maternity wards at the national hospital and the local health centre were invited to participate in the present study when their child was to receive BCG vaccination after delivery. Furthermore, mothers who delivered at home were invited to participate when they came for BCG vaccination at two of the three health centres in the study area (the third health centre was not included for logistic reasons). The inclusion criteria were weight ≥2500 g and no signs of overt illness. All infants were vaccinated intradermally in the upper left deltoid region with 0.05 ml BCG vaccine (Statens Serum Institut, Copenhagen, Denmark) [7].

Provided oral and written consent, the mother drew a lot from an envelope containing 100 lots deciding which supplement the child should receive: the intervention treatment consisting of 50,000 IU vitamin A as retinyl palmitate and 10 IU vitamin E in 1/2 ml vegetable oil, placebo was 10 IU vitamin E per 1/2 ml oil. The supplements looked alike, and small differences in taste and colour of the contents were judged as unimportant due to the recipients' age. None of the three assistants who were responsible for the randomisation procedures at the hospital and at the health centres knew which supplement contained vitamin A. The code was kept at the pharmacy until 12 months after the last child was enrolled [7].

All children were followed through the routine DSS every 3 months and were visited by a special team at 12 months of age. The DSS assistants and the special follow-up team were unaware of the allocated treatment, since they were not present during enrolment, 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 conducted by a trained local physician. No death was due to accident. All children were offered 100,000 IU vitamin A at the 12 months-visit [7].

2.3. Vaccination data

Since the BHP had provided BCG and early measles vaccinations, and registered OPV at birth, we had the best available data on these vaccinations. At the BHP, data on other vaccinations are gathered in several complementary ways. *First*, all vaccinations at the three health centres in the study area are registered on the day of vaccination. This covers more than 80% of the vaccinations received by children in the study area, but does not account for vaccinations

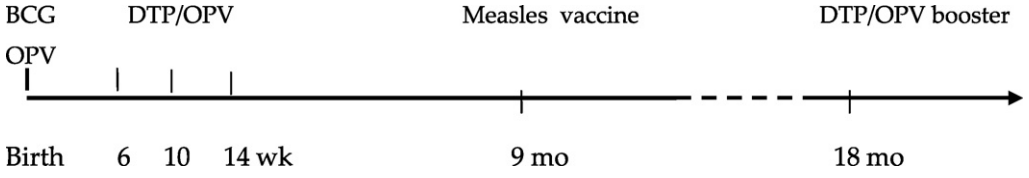

Fig. 1. Vaccination schedule in Guinea-Bissau.