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Original Article

Randomized trial: The effect of oral polio vaccine at birth on polio antibody titers at 6 weeks and 6 months of age ☆

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ABSTRACT

Background: In Guinea-Bissau we conducted a randomized trial of OPV0 versus No OPV0 to test the effect of not receiving OPV0 on infant mortality and morbidity. In two subgroups of participants, 6-week-old children and 6-month-old children, we investigated the effect of OPV0 on neutralizing antibodies against poliovirus type 1 and 3.
Design: A subgroup of infants randomized to receive OPV0 or No OPV0 in addition to the usual childhood vaccines were visited at home at 6 weeks or 6 months of age, and a blood sample was collected from the child and the mother.
Setting: Urban Guinea-Bissau.
Main outcome: Geometric mean titers (GMT) of neutralizing antibodies and seropositivity (titer ⩾ 1:8) for poliovirus type 1 and 3.
Results: OPV0 did not affect the overall seropositivity at 6 weeks or 6 months of age for either polio 1 or 3. In 6-week-old infants, not receiving OPV0 was associated with significantly lower GMT for polio 1 and 3 (GMT ratio = 0.52 (95% CI = 0.33–0.79) for polio 1; 0.44 (0.28–0.70) for polio 3), the effect being significant in its own right in boys and in children whose mothers had low antibody levels. In contrast, in 6-month-old infants, not receiving OPV0 was associated with significantly higher GMT for polio 1 (GMT ratio = 2.10 (1.32–3.35)). This was significant in its own right in boys and in children of mothers with high antibody levels.
Conclusions: OPV0 may contribute to early polio protection, particularly in children of mothers with low antibody levels. However, OPV0 did not contribute to overall polio immunity after subsequent doses of OPV were given, and was associated with significantly lower antibody titers in children of mothers with high antibody levels. However, it did not negatively affect the proportion of seropositive children.

Introduction

Oral polio vaccine (OPV) at birth was introduced to ensure early protection against polio and to increase coverage [1,2]. Studies have shown that OPV at birth (OPV0) increases antibody titers between birth and 6 weeks of age compared with No OPV0, but not after 4 months of age when the children have received three additional OPV doses (OPV1–3) [2,3]. The effect of OPV0 on overall child mortality and on the immune response to other vaccines was never studied.

In 2004 in Guinea-Bissau, two randomized trials were ongoing, testing the effect of neonatal vitamin A supplementation in normal-birth-weight children and the effect of BCG at birth to low-birth-weight children, respectively [4,5]. That year the country experienced periods when OPV was in short supply. Surprisingly, not receiving OPV0 was associated with significantly lower mortality in boys while it made no difference for girls [6]. At age 6 weeks, the *in vivo* and *in vitro* immune responses to BCG vaccine were

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reduced in infants who had received OPV0 with BCG compared to those who had only received BCG [7]. These effects were found in both sexes.

If OPV0 has negative effects on male mortality or on the immune response to BCG vaccine, it is essential to reassess the importance of OPV0 for polio immunity. Today, most pregnant women have been vaccinated against polio and have not experienced natural polio infection. Hence, they are likely to transfer lower levels of antibodies to their offspring which may increase the immunogenicity of OPV0 [8,9]. Also, the BCG vaccine administered simultaneously with OPV0 may influence the immune response to OPV [10].

Intestinal immunity to poliomyelitis correlates with serum antibody titer [11]. In the present study we assessed the effect of OPV0 provided with BCG at birth on polio antibody titers at 6 weeks of age and at 6 months of age.

Materials and methods

Setting

The study was conducted at the Bandim Health Project (BHP), Guinea-Bissau, which covers an urban area with a health and demographic surveillance system (HDSS) monitoring around 102,000 individuals. The recommended vaccination schedule is BCG and OPV0 at birth, three doses of pentavalent vaccine and OPV (OPV1–3) at 6, 10 and 14 weeks of age, and measles vaccine and yellow fever vaccine at 9 months of age.

Main OPV0 trial

Healthy normal-birth-weight children ($\geqslant$2.5 kg) less than 1 month old were eligible for the main randomized trial. Mothers giving birth at the national hospital or bringing their child for vaccination at one of the three local health centers were invited to participate before their child received BCG and OPV. The randomization to OPV0 or No OPV0 was stratified by sex. All children received BCG.

The present subgroup study

The study took place between August 18 and November 27 2009 and again from February 8 to April 22 2010. We bled two cohorts of children: A cohort of 6-week-old children and a cohort of 6-month-old children. Eligible were children enrolled in the main trial *within the first week of life* and who had not been included in a concurrent study examining *in vitro* cytokine responses. Children who had received a routine OPV1 before the recommended age of 6 weeks, and thus before the 6-week-sample, were not included in the 6-week cohort, to assure a pure comparison between No OPV0 and OPV0. Due to limited resources we were unable to recruit 105 of the eligible 6 week children and 23% of the eligible 6-month-old-children (Fig. 1). At enrolment the mother was bled as well, to assess maternal antibodies against polio type 1 and 3.

OPV campaigns

We planned to enroll children until May 2010, but from March 6–9 and again from April 24–27 2010, national polio immunization campaigns provided monovalent OPV directed against polio type 1 for all children aged 0–5 years. Since we aimed for a pure comparison between No OPV0 and OPV0 in 6-week-old children, we stopped including 6-week-old children on March 4 2010, before the first campaign. The enrolment of 6-month-old children continued, as the aim in this group was to study the long-term impact of No OPV0 in children who had received additional OPV. However, we stopped just before the second round as we had almost reached the sample size and were aware that OPV provided in the campaigns could dilute any effect. Hence, a subgroup of the 6-month-old children ($N = 83$) had received one dose of monovalent OPV during the campaign (cOPV). Information on cOPV was obtained on two occasions. First, immediately after the campaign BHP assistants visited all children in the study area and asked whether the child had received cOPV. If so, it was noted on the child's vaccination card. Second, at the time of the bleeding, the mother was asked once more, and the vaccination card was checked for consistency.

Sample size

We aimed to obtain 300 samples from children at the age of 6 weeks and 300 samples from children aged 6 months. However, we were not able to reach that target for 6-week old children due to the national polio immunization campaigns.

Laboratory methods

Capillary blood samples were collected in EDTA coated microtainers. Polio 1 and polio 3 neutralizing antibody titration assays were performed in duplicate using the standard polio neutralization assay described in the EPI manual, World Health Organization (WHO) 1997 [12], at a starting dilution of 1:8 and the assays were incubated for 5 days. The assays were read by three different operators. An internal standard, cell quality control and virus control were included for analysis of each batch of sample plasma. The internal standard was calibrated against the WHO international reference preparation. The geometric mean titer for the internal standard for polio type 1 and polio type 3 was 1:360 and 1:428, respectively, with a potency established by calibration of 21 IU for type 1 neutralizing antibodies and 7 IU for type 3 neutralizing antibodies, thus the sensitivity of the polio 1- and polio 3 assays were 58 and 16 mIU respectively. Dilutions of $\geqslant$1:8 were considered seropositive. If there was insufficient plasma, we prioritized the measurement of polio 1 antibody levels.

Statistical methods

Statistical analyses were carried out using STATA 10.1. *P*-values <0.05 were considered statistically significant. For background characteristics, categorical variables were compared using the χ^2 test and continuous variables were compared by Student's *t*-test. Mean and standard deviation (SD) were presented for continuous variables. For age which was not normally distributed, the median and the interquartile range (25–75 centile) were presented.

Seropositivity rates were calculated for each serotype. Seropositivity prevalence ratios were calculated using Poisson regression with robust variance estimates [13]. Geometric mean titers (GMT) were calculated for seropositive children (titer $\geqslant$ 1:8). To calculate the ratio between the GMT in the No OPV0 group and the GMT in the OPV0 group (the GMT ratio) a linear regression was conducted with the log-transformed titers as outcome and the randomization group as a covariate. The GMT ratio was obtained as anti-log (exp) of the coefficient for the group difference. Hence, a GMT ratio of 2 would mean that the GMT in the No OPV0 group was twofold higher than the GMT in the OPV0 group. GMT > 1:512 were set to 1:1024. Tobit regression was used to account for this right-censoring.

Both crude and adjusted analyses were conducted. The adjusted analyses included: sex, age at enrolment (0–1 days or 2–7 days), and season of enrolment (rainy season (June–November) or dry season (December–May)). These factors were included since randomization was stratified by sex, age is generally an import