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Measles antibody levels after vaccination with Edmonston-Zagreb and Schwarz measles vaccine at 9 months or at 9 and 18 months of age: A serological study within a randomised trial of different measles vaccines☆

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ABSTRACT

Standard–titre Schwarz (SW) and Edmonston-Zagreb (EZ) measles vaccines (MV) are both used in the routine immunisation programme. Within a trial of different strains of MV, we examined antibody responses in both one-dose and two-dose schedules when the first dose was administered at 9 months.

Setting and Methods: The trial was conducted in an urban area in Guinea-Bissau where we have had a health and demographic surveillance system and studied strategies to prevent measles infection since 1978. In the present study, children were randomised to SW or EZ as the first MV and furthermore randomised to a second dose of the same MV or no vaccine at 18 months of age. We obtained blood samples from 996 children at baseline; post-vaccination blood samples were collected at 18 and 24 months of age to assess measles antibody levels after one or two doses of MV.

Results: At age 18 months all had responded to the first dose and only 1% (8/699) of the children had non-protective antibody levels irrespective of vaccine type. SW was associated with significantly higher levels of measles antibodies (geometric mean titre (GMT) = 2114 mIU/mL (95%CI 1153–2412)) than EZ (GMT = 807 mIU/mL (722–908)) ($p = 0.001$). Antibody concentration was significantly higher in girls than in boys after EZ but not after SW. Antibody levels were higher in the rainy than the dry season. There was no clear indication that a booster dose at 18 months increased the antibody level at 24 months of age.

Conclusions: Maternal antibody levels have declined significantly in recent years and 99% had protective levels of measles antibody following primary MV at 9 months of age. It is unlikely that measles prevention and child health will be improved by increasing the age of MV as currently recommended.

1. Background

The two measles vaccines (MV) most commonly used in low-income countries are standard-titre Schwarz (SW) and Edmonston-Zagreb (EZ) vaccine. After discontinuation of high-titre MV [1], two-dose MV schedules were suggested to lower the age of MV [2]. From 1995 to 2002, all children in the Bandim Health Project (BHP) study area in Bissau were offered enrolment in an early two-dose MV trial from 6 months of age [3–6]. The two-dose schedule increased coverage considerably and provided better protection against measles among infants than one-dose at 9 months of age schedule [4]. EZ and SW MV were used for different cohorts within the trial and EZ MV seemed to provide a better booster response than SW MV [5]. We have therefore been interested in comparing EZ and SW MV in a randomised trial of two-dose schedules.

According to WHO and UNICEF plans all children should be guaranteed a second opportunity for MV either through campaigns or routine immunisation [7]. In Latin America, MV campaigns have been introduced to support routine immunizations and the administration of the first vaccine has been postponed to 12 months because seroconversion is believed to be better after 12 months of age [8]. It has been suggested to increase the age of vaccination in other regions when measles comes under control [9]. An increase

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in age of primary MV could dramatically enlarge the number of susceptible infants in crowded urban areas in Africa [10,11]. Many observational studies and a few randomised trials have indicated that MV has non-specific beneficial effects by providing protection against other infections than measles, in particular against lower respiratory infection [3,6,12–15]. Increasing the age of administration would therefore limit the beneficial non-specific effects of MV. Thus finding the best schedule and vaccine strain for use in a routine two-dose schedule might be the best approach for the African region. We have therefore conducted studies of both early (4½ and 9 months) and later (9 and 18 months of age) two-dose MV strategies [11,14]. In the present paper we compare the antibody response of standard-dose EZ and SW MV when administered at 9 and 18 months of age.

2. Methods

2.1. Setting

The trial was conducted at the Bandim Health Project (BHP), which has a demographic surveillance system in several districts of the capital of Guinea-Bissau between 2003 and 2007. The current population is around 102,000. All houses are visited every month to register new pregnancies and births. The BHP field-workers visit all children every 3 months until the age of 3 years to collect information on breastfeeding patterns, infections, hospitalisation, vaccinations, and socio-economic characteristics.

2.2. Study design

The present serological study initiated in 2004 was part of a randomised trial [11,14]. Children were enrolled at 4.5 months and randomised to one of three groups: Group I received EZ MV at 4.5 and 9 months, Group II SW MV at 9 months, and Group III EZ MV at 9 months of age. At 9 months of age the children were invited back to one of the three health centres in the study area; Group I received a second dose of EZ MV, Group II received their first dose of SW MV, and group III the first dose of EZ. At 18 months children from groups II and III were invited back. If the mothers consented, the children were randomised to receive a second dose of the same strain of MV or no second dose of MV (Supplementary Fig. 1). The present analysis deals only with groups II and III.

2.3. Enrolment

Newborn infants were identified in the BHP register. To make sure that all children had received three doses of diphtheria, tetanus and pertussis (DTP) vaccine four weeks before inclusion in the trial, we contacted mothers of children aged 6, 10 and 14 weeks, and reminded them to go to the local health centre to receive the oral polio vaccine (OPV) and DTP vaccine. Children were enrolled at 4.5 months of age. In the morning a field-worker contacted the mothers/guardians of eligible children, explained the study, filled in a questionnaire on background factors, and obtained verbal consent. Mothers were asked to bring their children to the health centre in the afternoon. The trial physician provided attending mothers/guardians with an oral and a written explanation of the study. At each health centre visit the children were examined by the physician. Clinical examination and treatment was independent of randomisations group. Children who were sick and needed admission to hospital could only participate when they had recovered.

2.4. Randomisation and intervention

The data manager, who was not involved in enrolment procedures, prepared bags with 24 numbered envelopes indicating the randomisation group. These numbers could not be seen by the physician informing and obtaining consent from the mothers/guardians. Following consent the mothers/guardians were asked to select one envelope. We used block randomisation with 24 envelopes per bag.

2.5. Measles vaccines

Standard-titre EZ MV from the Serum Institute of India, Pune, India, (batch 2360) and standard-titre SW MV (Rouvax) from Aventis, France, (batch w5556-1, wx5491-2) were used. MV was administered subcutaneously with 23G needles in the upper part of the back. No other vaccine was given at the same time.

2.6. Sample size

We needed 400 children per group to detect a 10% difference in the proportion of non-seroconverters.

2.7. Blood sampling and antibody analysis

We collected blood samples at 9, 18 and 24 months in Group II and III. The mothers were sampled at the first contact. The 9 month sample was a pre-vaccination sample and should mainly reflect maternal antibody levels. The sample at 18 months was collected prior to a possible second dose of MV and was therefore used to assess antibody levels after the first dose of MV at 9 months of age. The sample at 24 months of age was intended to measure long-term maintenance of antibody levels and to examine the possible booster effect of a second dose of MV.

Samples were analysed by the measles haemagglutination inhibition test (HAI) at the MRC Laboratories in Gambia [16,17]. Sensitivity was 15.6 mIU/mL and with a starting 1:2 dilution, the minimum detectable titre was 31.2 mIU/ml. The protective antibody level is 125 mIU/mL, a positive reading in the 1:8 dilution. Children with 31–63 mIU/ml have low non-protective measles antibody levels.

2.8. Measles epidemic and antibody levels

The study area experienced a measles epidemic between May 2003 and May 2004. Since the antibody started in March 2004 some of the first children enrolled in the serological study may have had clinical measles or subclinical measles [11,18]. There was no measles infection when the 18 and 24 months samples were collected. The children with clinical measles have been excluded from the analysis (see Supplementary Fig. 1). The level of measles antibody after subclinical infection is difficult to define. However, we have assumed that most children who had protective measles antibody levels at 9 months of age (see Supplementary Fig. 1) were likely to have locally produced antibodies after subclinical infection rather than (high) maternal measles antibody [18]. This interpretation is supported by several lines of evidence, first, the mother of children who had “protective level at 9 months” did not have higher antibody levels than mothers of children with non-protective levels at 9 months; second, whereas girls had lower level of maternal measles antibody levels at 4.5 months of age than boys, they had higher levels than boys at 9 months of age, and only subclinical infection seems to able to explain this inversion in the antibody levels of girls and boys; and third, following vaccination at 9 months of age, children with “protective level at 9 months” continued to have a high level at 18 and 24 months of age which was presumably due to boosting of acquired immunity by subclinical infection (see below). Had the high level at 9 months been due to maternal measles antibody, we should have seen a reduced