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Vaccination status and sequence of vaccinations as risk factors for hospitalisation among outpatients in a high mortality country

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ABSTRACT

Background: Most developing countries are implementing the WHO immunisation programme. Although vaccines reach most children, many modifications of the recommended schedule are observed in practice. We investigated the association between vaccination status and risk of hospitalisation in Guinea-Bissau.
Methods: From May 2003 to May 2004, all consultations of children less than five years of age at the outpatient clinic of the paediatric ward at the national hospital in Bissau were registered. For each consultation, information was collected about the child's name, sex, age and socio-cultural conditions, as well as diagnosis and whether the child was hospitalised. Information about vaccinations was also registered from the child's vaccination card. We analysed the association between vaccination status and risk of hospitalisation in age intervals according to the pre-dominant vaccines. We particularly emphasised the comparison of those who had received the recommended vaccination for the age groups and those who were delayed and only had the previous vaccinations. We also examined those who had received the vaccines out of sequence.
Results: Information about vaccinations was available for 11,949 outpatient children of whom 2219 (19%) were hospitalised. Among children less than 3 months of age, unvaccinated children compared to BCG children had as expected a higher risk of hospitalisation; controlled for important determinants of hospitalisation, the hospitalisation risk ratio (HRR) was 1.99 (95% CI 1.37–2.89). In contrast, there was no difference in the HRR for children aged 1½–8 months who were delayed and had only received BCG compared to those who as recommended had received diphtheria–tetanus–pertussis (DTP) vaccine after BCG (HRR = 1.10 (0.77–1.59)). In the age interval 9–17 months of age, children who were delayed and had only received DTP had significantly higher risk of hospitalisation compared with children who as recommended had measles vaccine (MV) as the most recent vaccination (HRR = 1.39 (1.16–1.66)). Having received DTP after MV (HRR = 1.60 (1.15–2.24)) or MV and DTP simultaneously (HRR = 1.51 (1.16–1.97)) was also associated with higher risk than MV only as most recent vaccination. In contrast, the children aged 18–59 months who as recommended had received a DTP booster after MV did not have lower risk of hospitalisations compared with children who were delayed and had received only MV (RR = 0.90 (0.75–1.07)). After 9 months of age, there was a significant difference in the female–male HRR for children who had MV (HRR = 0.85 (0.72–1.00)) or DTP (HRR = 1.08 (0.96–1.22)) as most recent vaccination ($p = 0.02$, test of interaction).
Conclusion: Following the recommended vaccination schedule for BCG and MV is associated with a reduced risk of hospitalisation but this is not the case for DTP and booster DTP. Receiving DTP simultaneously with MV or after MV is associated with increased risk of hospitalisation. Vaccines have sex-differential effects on the risk of hospitalisation.

1. Introduction

Immunisation remains one of the most important public health interventions and cost effective strategies to reduce both the morbidity and mortality associated with infectious diseases [1]. Almost all African countries have adopted the WHO recommendations and introduced the Expanded Program on Immunisation [EPI] programme as one of the main public health strategies. Guinea-Bissau is a country with very high childhood mortality, infant mortality being 138 and under five mortality being 223 per 1000 live births [2]. Guinea-Bissau adopted the EPI activities to prevent childhood deaths in 1985 [3]. At the time of the present study, the WHO

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EPI programme recommended BCG and oral polio vaccine (OPV) at birth, three doses of diphtheria–tetanus–pertussis (DTP) and OPV at 6, 10, and 14 weeks of age, and measles vaccine (MV) at 9 months of age. Furthermore, some countries including Guinea-Bissau have used booster doses of DTP and OPV at 18 months of age [4].

The uptake of vaccinations is dependent not only on provision of vaccination services and the availability of vaccines but also on other factors including knowledge and attitude of mothers [5,6], access to health workers [7], cost of access to vaccination clinics, and availability of needles and syringes. Thus, in African countries, the formal schedule is often not followed and the sequence of vaccinations may vary considerably [8]. In Guinea-Bissau, the sequence is often not followed because the mother was travelling, had no money to pay for a vaccination card, the local health centre did not want to open a bottle of BCG for just one child, the child was sick, or vaccines were not available [8,9]. Therefore vaccines, which should have been administered in sequence, are often administered simultaneously or in the wrong sequence.

There is growing recognition that vaccinations may have non-specific effect (NSE) for child health and survival [10–12]. Hence, there is a need to study how vaccines and the sequence of vaccinations affect the severity of infections among children. Previous studies have shown that BCG and MV as most recent vaccination has a beneficial effect on child survival [13–17]. These effects have also been shown in randomised clinical trials [18,19]. On the other hand, DTP as most recent vaccination may not have a beneficial effect on child mortality and morbidity, particularly for girls [4,8,14,15,17,20–22]. In the present study we examined whether the vaccination status, including the sequence of vaccinations, among outpatients at the national paediatric ward was related to the likelihood of being hospitalised.

2. Subjects and methods

2.1. Health care system in Guinea-Bissau

The first contacts for the health system are the health centres (HCs) where the personal are nurses and sometimes physicians. Routine vaccinations and other preventive care as well as curative care are provided at the HCs. Several regions in Guinea-Bissau have a regional hospital, and the hospital in Bissau, Simão Mendes, is the national referral hospital. However, in Bissau, many HCs function with deficiency or not at all; hence, many mothers go directly to the national hospital for consultation. Routine childhood vaccinations are delivered only at HCs supplemented by regular outreach vaccination campaigns.

2.2. Paediatric ward

The paediatric department at the national hospital is the national referral paediatric ward. Most patients, especially those living in Bissau, use the department as their primary contact. The annual number of admissions is around 5000–6000.

In connection with a study of consultations between May 2003 and May 2004 [23] funded by the Gates Malaria Partnership/LSHTM, we registered all children less than 5 years of age consulting at the Out-Patient Department (OPD) and hospitalised at the paediatric ward at Simão Mendes to examine the possible impact of vaccination status on hospitalisations. For each consultation, information was collected about the child's name, sex and age, whether the child had a health card, vaccination status, diagnosis and whether the child was hospitalised. Information about ethnicity and socio-economic conditions was also collected. Data on outpatients were collected and entered by a separate team not linked to the routine team monitoring mortality at the paediatric ward [4,8,24].

2.3. Vaccination status

Information on vaccination status was obtained by a field worker from the vaccination card at the first consultation [4,8,9]. Children were classified as vaccinated with a specific vaccine if there was a date indicated on their vaccination card. Children were classified as "unvaccinated" if their cards had been seen at consultation and no dates of vaccination were indicated, or as vaccination status "unknown" if their card had not been seen.

2.4. Analytical strategy

We excluded children with missing information with respect to date of birth or hospitalisation. Children referred from another health unit were treated separately as they are likely to belong to a group with different vaccination coverage. The present study only included children who had information on vaccination.

First, we determined risk factors for hospitalisation in the BCG and DTP dominated age interval from 8 days to 8 months of age, and in the MV dominated age interval from 9 to 17 months of age. A risk factor was considered significant if it, controlled for all other potential risk factor, was statistically significant with $p < 0.1$.

Secondly, we analysed the possible impact of different vaccines and sequences of vaccinations in four age intervals: the BCG dominated age interval between 8 days and 3 months of age, the DTP dominated age interval between 6 weeks and 8 months of age (Fig. 1), the MV dominated age interval from 9 months to 17 months of age, and the DTP-booster dominated age interval from 18 months of age and above (Figs. 2 and 3). Analyses were controlled for the general risk factors found to be significant in the initial analyses.

Thirdly, the exclusion of referred cases and the inclusion of measles cases could have affected the results. We therefore present additional estimates for vaccination status and risk of hospitalisation for referred cases. We also estimated the HRR after exclusion of measles cases from the main analysis. However, this did not change the estimates and the results have therefore not been shown. It is likely that it will take several days before the immunological profile of a child changes following a new vaccination [21,22] and we therefore examined whether exclusion of children who had received the most recent vaccination within the last two weeks mattered to the estimates. In general, exclusion of the most recent vaccinations within 14 days had no impact and results are therefore not shown.

Like measles infection, whooping cough epidemics could have affected the relative severity of the infections of DTP-vaccinated and DTP-unvaccinated and therefore biased the comparison of DTP-vaccinated and DTP-unvaccinated children. However, herd immunity for pertussis is high due to high vaccination coverage in Bissau and there were no diagnosed cases of whooping cough among hospitalised children. The potential impact of whooping cough has therefore not been further controlled.

For each age interval, we compared the hospitalisation risk ratio (HRR) for the children who had received the recommended vaccination as most recent vaccination in relation to children who were delayed and had not yet received the recommended vaccination. Numerous studies from Bissau have shown that healthier children are likely to get vaccination first and to follow the recommended sequence of vaccination [14]. One might therefore expect that the children following the official schedule would be less severely sick and therefore less likely to get hospitalised. On the other hand, socio-economic and educational conditions and sex-differential