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Contrasting female-male mortality ratios after routine vaccinations with pentavalent vaccine versus measles and yellow fever vaccine. A cohort study from urban Guinea-Bissau

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ABSTRACT

Background: In addition to protection against the target diseases, vaccines may have non-specific effects (NSEs). Measles vaccine (MV) has beneficial NSEs, providing protection against non-measles deaths, most so for girls. By contrast, though protecting against diphtheria, tetanus and pertussis, DTP vaccine is associated with increased female mortality relative to male mortality. In 2008, Guinea-Bissau replaced DTP with the DTP-containing pentavalent vaccine (Penta; DTP-H. influenza type B-Hepatitis B) at 6, 10 and 14 weeks and yellow fever vaccine (YF) was to be given with MV. We investigated possible sex-differential mortality rates following Penta and MV+YF vaccination.

Methods: Bandim Health Project (BHP) registers vaccines given by the three government health centres in the study area and vital status through demographic surveillance. We assessed the association between sex and mortality by vaccination status in Cox proportional hazards models with age as underlying timescale. Follow-up was censored at a subsequent vaccination contact or after 6 months of follow-up.

Results: Between September 2008 and April 2011, we registered 23,448 vaccination contacts for children aged 42–365 days; 17,313 were for Penta and 3028 for MV (2907 co-administered with YF). During follow-up 112 children died. The female/male mortality rate ratio was 1.73 (1.11–2.70) following Penta and 0.38 (0.12–1.19) after MV (p = 0.02 for same effect). Adjusting for maternal education or weight-for-age at the time of vaccination did not change the estimates.

Conclusion: Penta appears to have the same negative effects on mortality as those seen for DTP. Assessing post-vaccination mortality for boys and girls is necessary to improve the vaccination programme.

1. Introduction

Vaccines are given to prevent specific infections but there is increasing evidence that vaccines may have much broader effects on overall child health [1]. The effects which are not explained by specific disease prevention have been named "non-specific" or "heterologous". While disease-specific immune memory may not be altered by administration of subsequent vaccines, the non-specific effects (NSEs) are shaped most strongly by the most recent vaccination [2–4].

The NSEs can be beneficial but also harmful. The live Bacillus Calmette-Guerin (BCG) and measles vaccine (MV) are associated with beneficial NSEs improving overall child survival [5–12]. However, though protecting against the targeted infections, the inactivated diphtheria-tetanus pertussis vaccines (DTP) is associated with higher child mortality [3,5,12–17]. NSEs are often sex-differential; while MV has been associated with stronger beneficial effects for girls than for boys, DTP has been linked to higher female mortality [2,3,6,13,18,19]. In low-income countries, vaccines are recommended sequentially during infancy: BCG vaccine at birth, three doses of DTP-containing vaccine at 6, 10 and 14 weeks of age and a MV at 9 months of age. If DTP and MV have strong effects

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on child survival, changing from having DTP to having MV as the most recent vaccine should lower the female/male mortality rate ratio (F/M MRR). In 2007 this lead to the formulation of the hypothesis, that the transition from DTP to MV should result in an inversion of the F/M MMRs [20].

During the last 10 years the DTP-containing pentavalent vaccine ("Penta": DTP-H. influenza type B-Hepatitis B) has replaced DTP [21] and yellow fever vaccine (YF) has been introduced to be co-administered with MV [22] in many low-income countries. Hence, we investigated whether the F/M MRR after Penta and after MV+YF were similar to the effects previously reported for DTP and MV.

2. Methods

2.1. Setting and population

Bandim Health Project (BHP) runs a Health and Demographic Surveillance system (HDSS) in six suburban districts in Bissau, the capital of Guinea-Bissau. The HDSS covers a population of 100,000 individuals. All households are visited monthly to enquire about pregnancies and deaths. At the first visit after birth information on socioeconomic status is collected. The indicators include maternal characteristics (education and ethnicity) and household characteristics (type of roofing, availability of bathroom and electricity). Children below the age of 3 years are visited every 3 months to collect information on vital status as well as vaccinations, hospitalisations and nutritional status.

2.2. Assessment of exposure

Since the end of August 2008, the national Expanded Programme on Immunizations (EPI) vaccination schedule in Guinea-Bissau is BCG and OPV at birth, Penta with OPV at 6, 10 and 14 weeks and MV and YF vaccine at 9 months of age [23]. Vaccinations are administered at the three health centres in the study area and during outreach campaigns with occasional vaccination posts outside the health centres. A BHP-assistant records all vaccinations and weighs all children presenting for vaccination using an electronic scale (SECA 835/SECA 336).

2.3. Assessment of outcome

Mortality was assessed at all home visits. After registration of a death a verbal autopsy [24] was conducted by a trained field assistant. A medical doctor subsequently reviewed the collected information to assess the cause of death.

2.4. Interventions taking place during the study period

A full list of campaigns with vitamin A and vaccinations which were conducted during the study period is provided in Supplementary Table 1. In July 2009, children aged 9 months-5 years received MV; OPV was given to children 0–5 years in March, April and May 2010 and in March and April 2011. In October 2010 an H1N1 influenza vaccination campaign targeted children aged 6 months to 5 years.

Three randomised trials (RCTs) could have affected the study cohort. One RCT compared OPV+BCG vs BCG-only among normal birth weight children (enrolled neonates between July 2008 and October 2011) [25]; another RCT compared delayed BCG (current practice) vs. BCG at birth to low birth weight children (enrolled neonates between February 2008-September 2013) [26]. A third RCT compared vitamin A supplementation (VAS) versus placebo at vaccination contacts after 6 months (enrolled children aged 6–23 months between August 2008-December 2009) [27].

2.5. Epidemiological and statistical methods

Our main interest was the F/M-MRR after Penta (which was defined as a Penta ±OPV) and MV+YF, respectively. A child resident in the BHP HDSS and aged 42 and 365 days could enter the analysis on the date of vaccination at a health centre/outreach post in the study area. We excluded vaccination contacts at which VAS was given, as it was pre-specified that the hypothesis regarding female-male differences in mortality after DTP and MV should be tested in settings where no other interventions were given [20] and we have shown in many previous studies that vitamin A and vaccines interact [28–30].

Baseline characteristics were compared by sex within vaccine groups. We calculated a weight for age-Z-score (WAZ) for the vaccinated children using the 2006-WHO child growth standard [31] and the WHO Anthro version 3.2.2 macro for Stata [32].

We compared the survival of girls and boys in Cox-proportional Hazards models with age as the underlying timescale. Children entered the survival analysis at dates of vaccination between 1 September 2008 and 18 April 2011. The study was terminated at 18 April 2011 because children receiving Penta after this date were likely to enter a RCT of early MV at 4.5 months of age (clinicaltrials.gov, NCT 01486355). Analyses were conducted using Stata13.0.

As discussed above, the NSEs are strongest for the most recent vaccine. Therefore a child contributed survival time with a given vaccine until the reception of a subsequent vaccine or for a maximum of 6 months, as pre-specified in the hypothesis [20]. Hence, follow-up was censored when children received a different vaccine. The children could re-enter the analysis in a new vaccination group according to a subsequently received vaccine. All analyses of Penta were additionally censored at 9 months of age, since children become eligible for MV at 9 months of age, and prolonging follow-up beyond that date would inevitably accumulate more follow-up time in children who were delayed for MV compared with children who received MV, creating the possibility for selection bias. Furthermore, we additionally censored at the first vaccination campaign occurring during the follow-up period. We stratified the analysis for participation in one of the neonatal trials. Previous studies have suggested, that early administration increases the negative effect of DTP [3,33]. In the 1980s, DTP was only given from 3 months of age [14]; we assessed whether sex-differential mortality patterns after Penta depended on age at vaccination. Finally, we assessed whether excluding the first 4 months after the introduction of Penta and YF, where outreach campaigns were frequent and children received vaccines out of sequence, altered the results.

These analyses are based on children who presented for vaccination at the health centres/outreach posts in the study area. To obtain an estimate of the F/M MRR among children who were unlikely to have been Penta-vaccinated, we compared mortality by sex among children who had not (yet) presented for any vaccination after 42 days. This was done by linking the routine surveillance database with the health centre vaccination records, allowing all children under BHP surveillance between 1st September 2008 to 18th April 2011 to contribute to the analysis. In this analysis, children contributed time at risk between whichever came last: date of registration, date of birth and 1st September 2008, and until whichever came first: any registered vaccination contact after 42 days, migration or death. We compared mortality of girls to the mortality of boys in a Cox-proportional hazards model with age as underlying timescale. The F/M MRR was estimated in three age intervals: birth to 41 days, 42 days to 8 months and 9 (274 days) to 18 months. In the age group "birth to 41 days" the