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Short communication

Non-live pentavalent vaccines after live measles vaccine may increase mortality

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ABSTRACT

Live measles vaccine (MV) may have beneficial off-target/non-specific effects (NSEs) reducing child mortality beyond prevention of measles infection. In contrast, the non-live pentavalent (Diphtheria-Tetanus-Pertussis-*H. influenzae* Type B-Hepatitis B) vaccine has no beneficial NSEs. The NSEs are strongest for the most recent vaccine. Hence, sequence of vaccination may affect survival. In Guinea-Bissau, we followed 7094 measles-vaccinated children prospectively from first home visit after 9 months (when MV is scheduled) to 5 years of age. We compared survival by sequence of MV and third Pentavalent vaccine (Penta3; scheduled at 3½ months) in Cox proportional-hazards models. Compared with being vaccinated in-sequence (Penta3-then-MV), having received out-of-sequence Penta3-after-MV before the visit was associated with an adjusted Hazard Ratio (aHR) of 1.19 (95%CI: 0.84–1.69); Receiving missing Penta doses on the visit date tended to be associated with higher mortality (aHR = 1.87 (0.96–3.65)) while not receiving missing doses of Penta was not (aHR = 0.93 (0.57–1.54)), test for interaction p = 0.09.

1. Introduction

The Expanded Programme on Immunizations (EPI) in many low income countries includes Bacillus Calmette-Guérin vaccine (BCG) with oral polio vaccine (OPV) at birth, 3 doses of diphtheria-tetanus-pertussis (DTP)-containing vaccine with OPV at 6, 10 and 14 weeks of age and measles vaccine (MV) at 9 months of age [1]. Since three doses of DTP-containing vaccines are scheduled, delays in DTP-vaccinations frequently accumulate and cause DTP-containing vaccines to be given after MV. The actual sequence of vaccinations receives little focus in the present monitoring of the EPI. EPI performance is assessed by coverage for specific antigens; administrative data reported to donors and WHO focus on the number of doses given to infants [2]. It is assumed that providing missing vaccine doses will always leave the child better off than not providing them. However, this may be wrong.

In addition to preventing targeted infections, vaccines may have non-specific effects (NSEs) affecting susceptibility to unrelated infections. In the recent WHO-commissioned review of the NSEs of the live attenuated BCG and MV and the non-live DTP-vaccine, there were strong contrasts between the live vaccines, which were associated with 40–50% lower mortality, and the non-live DTP vaccine, which tended to be associated with higher mortality [3]. The review also indicated that sequence of vaccines was important: compared with the recommended sequence (MV after DTP), DTP after MV was associated with 2.66 (95%CI: 1.04–6.81) times higher mortality and DTP with MV was associated with a 2.29 (1.55–3.37) times higher mortality [3]. A new study of vaccination sequence and mortality from Ghana found that mortality for children who received DTP-containing vaccines after MV was 1.61 (1.07–2.44) times higher than for children vaccinated in-sequence [4].

We took advantage of the continuous data collection of the Bandim Health Project (BHP) to assess associations between vaccination sequence and subsequent mortality. Higher mortality of children receiving vaccines out-of-sequence could be due to an inherent bias, the mothers being less compliant with the health care system. In the present study, we could assess mortality of children who received out-of-sequence vaccination, and mortality of children who were eligible for out-of-sequence vaccination but did not receive missing doses of DTP-containing vaccines.

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2. Methods

Setting: BHP runs a Health and Demographic Surveillance System (HDSS), covering 182 village clusters in Guinea-Bissau [5]. All households in the HDSS are visited every 6 months by field teams collecting information on women and children < 5 years. At all visits, pregnancies, births and deaths are registered; children are followed with registration of vital status, nutritional status (mid-upper-arm circumference) and vaccination status. A team nurse provides vaccines according to the national EPI. If a child died, an interview on symptoms and health seeking behaviour in the period leading up to the death is performed.

In August 2008, the pentavalent vaccine ("Penta", *DTP-Hepatitis B-H. influenzae type B*) was introduced in the EPI in Guinea-Bissau [5] and in June 2015, pneumococcal vaccine was introduced. Hence, between 2008 and 2015, the EPI schedule in Guinea-Bissau was BCG and OPV at birth, Penta and OPV at 6, 10 and 14 weeks, and MV and yellow fever vaccine at 9 months.

Study population and exposures: Measles-vaccinated children aged 9–18 months were included if they were present and had their vaccination card inspected at the first visit after 9 months of age between 1 September 2008 and 22 June 2015. We excluded children, who due to trials in the village clusters [6–8], were not eligible for the national EPI: children who received VAS in a trial of VAS at vaccination contacts [6] and children randomised to follow different MV schedules [7] (Supplementary Fig. 1).

Measles-vaccinated children were classified in four groups according to their Penta3-status and Penta3-MV-sequence. Two groups were Penta3-vaccinated. The first group had received MV and Penta3 in the recommended sequence, i.e., Penta3 before MV and MV as the most recent vaccine. The second group had not received vaccinations in the recommended sequence and therefore did not have MV only as the most recent vaccine. Two other groups had not yet received Penta3 on the date of the visit. These were divided in children, who received Penta and children, who did not receive Penta on the date of visit. Not all children who had not received Penta3 were offered vaccination, because Penta vaccines were not available, or because the national EPI restricted vaccination to children below 12 months or to children who had received their first Penta before 12 months.

Analyses: We compared mortality of measles-vaccinated children according to vaccination group in Cox-proportional hazards models with age as the underlying timescale. Children entered the analysis on the date of visit and were followed prospectively through the HDSS routines; observation time was censored at migration, 5 years of age or on 22 June 2015, whichever came first. The confidence intervals of the estimated Hazard Ratios (HRs) were adjusted for village cluster using robust standard errors, and HRs adjusted for period, region and maternal education were estimated.

3. Results

Among 25,831 children first visited at 9–18 months of age between 1 September 2008 and 22 June 2015, 7094 had received MV without co-administered VAS through the national EPI (Supplementary Fig. 1, Supplementary Table 1). The majority of the children (6458 (91%)) had already received Penta3 and among these 5426 (85%) had received Penta3 before MV, thus being vaccinated in-sequence (Table 1, Group 1). The 1032 children who were fully vaccinated but received vaccines out-of-sequence mainly had Penta3 with or after MV (co-administered Penta and MV: 780, Penta after MV: 177) as the most recent vaccine, but a smaller group had other vaccines (75; mainly OPV) (Table 1, Group 2). Nine percent of the children (636/7094) were Penta3-unvaccinated (Table 1, Groups 3 and 4). Among the 636 Penta3-unvaccinated children, 134 (21%) were given a missing dose of Penta at the home visit. There were significant differences in the distribution of the vaccination groups by period of study, region and maternal education as well as mid-upper-arm circumference for age [9], which may be an intermediate variable (Supplementary Table 2).

During follow up, 160 died among the 5426 (3%) children who were both measles and Penta3-vaccinated in-sequence (Group 1). Among children who had received vaccines out-of-sequence (Group 2), 43/1032 (4%) died resulting in a crude HR of 1.37 (0.96–1.95) compared with Group 1. Adjusting for region, period and maternal education the HR was 1.19 (0.86–1.69). Mortality in measles-vaccinated but Penta3-unvaccinated children (Group 3) was 17/502 (3%), similar to mortality in children vaccinated in-sequence (Group 1): crude HR = 1.06 (0.65–1.73), adjusted HR (aHR)=0.93 (0.57–1.54). However, mortality among children receiving Penta on the date of visit (Group 4: 10/134; 7%) was markedly higher compared with Group 1, crude HR = 2.26 (1.17–4.38), aHR = 1.87 (0.96–3.65) (Table 1).

According to the short interviews on the circumstances surrounding the death, 10 deaths (Group 1: 7, Group 2: 2 and Group 4: 1) were classified as accidents. Censoring deaths due to accidents did not alter the conclusions (Supplementary Table 3). Using shorter follow-up periods of 6 and 12 months, in which the children would be less likely to receive additional vaccines during follow-up, or censoring at vaccination campaigns, resulted in the same conclusions, but data are sparse and the confidence intervals became wider (Supplementary Table 3). There was no indication that the effect of receiving Penta after MV was particularly bad for girls with the full follow-up (Table 2). However, with the shorter follow-up periods, a stronger mortality difference for girls than for boys became evident: with 6 months of follow-up the adjusted estimate in girls receiving a missing dose of Penta was 5.10 (1.02–25.4) compared with girls who were fully vaccinated in-sequence, while the corresponding estimate in boys was 1.51 (0.20–11.2) (Table 2).

Table 1
Mortality among measles-vaccinated children according to vaccination status.

Vaccination group[a]	N	Mortality rate/1000 PYRS (Deaths/PYRS)	Crude hazard ratios[a] (95%CI)	Adjusted hazard ratios[b,c] (95%CI)
Group 1: Prior Penta3, then MV as most recent vaccine[d]	5426	11.3 (160/14,186)	1 (Ref)	1 (Ref)
Group 2: Prior Penta3, but did not have MV alone as most recent vaccine[e]	1032	15.1 (43/2847)	1.37 (0.96–1.96)	1.19 (0.84–1.69)
Group 3: No prior Penta3, not given Penta at visit[f]	502	11.1 (17/1537)	1.07 (0.65–1.75)	0.93 (0.57–1.54)
Group 4: No prior Penta3, given Penta at visit[f]	134	23.3 (10/430)	2.26 (1.16–4.39)	1.87 (0.96–3.65)

[a] MV: Measles vaccine; Penta3: Third dose of pentavalent vaccine. All children had received MV.
[b] Hazard Ratios estimated in Cox-model with age as the underlying timescale and cluster robust standard error.
[c] Adjusted for region of residence (North: Oio, Biombo and Cacheu; East: Gabu and Bafata; South: Tombali and Quinara and Islands: Bubaque and Bolama), Period and Maternal education (163 children with missing information on maternal education coded in a separate category. Setting these 163 as children of mothers with or without education had no effect on conclusions).
[d] MV alone or MV with yellow fever vaccine and/or oral polio vaccine as most recent vaccine.
[e] Penta3 before visit, but did not have MV alone or with yellow fever vaccine and/or oral polio vaccine as most recent vaccine.
[f] Restricting the analysis to the 636 Penta3-unvaccinated children for whom MUAC may be a considered a baseline measurement, the HR comparing Group 4 vs. Group 3 was 2.03 (0.92–4.45) adjusted for Region, Period, Maternal education and MUAC-for-age (22 children with missing MUAC-for-age assigned group median).

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