Tropical Medicine and International Health doi:10.1111/j.1365-3156.2005.01479.x

VOLUME 10 NO 10 PP 956–960 OCTOBER 2005

Non-specific effects of vaccination on child survival? A prospective study in Senegal

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Summary

OBJECTIVES Several studies have shown an association between vaccination and child mortality in developing countries. The present paper examines this issue using data from a Senegalese rural area which has been monitored from 1983 to the present.

METHODS We analysed two birth cohorts, comprising 7796 and 3573 persons who had received either BCG and DTP (diphtheria-tetanus-pertussis) simultaneously or neither of these vaccines, and who had been followed from birth to 2 years of age. The association between vaccinations and mortality was assessed by Cox proportional hazards model.

RESULTS Mortality ratios for recipients of the BCG/DTP combination were 0.59 (95% CI: 0.46–0.74) for the first cohort and 0.70 (0.50–0.97) for the second cohort. Mortality ratios for measles vaccine recipients were 0.98 (0.75–1.27) for the first cohort and 0.87 (0.57–1.30) for the second cohort.

CONCLUSIONS The BCG/DTP combination was associated with a reduction in mortality whereas measles vaccination was not associated with mortality.

keywords vaccines, diphtheria-tetanus-pertussis, measles, mortality, Senegal, Africa

Introduction

In addition to their individual and collective protective effect against the disease towards which they are targeted, vaccines are believed to have non-specific effects on human health. In particular, a number of studies have shown an association between measles vaccination and reduced child mortality in developing countries (Koenig *et al.* 1990; Desgrées du Loû *et al.* 1995; Aaby *et al.* 1995, 2003). As these studies were not randomized experiments, it is not clear whether vaccines have a biological effect or whether they are merely indicators of greater parental concern or better access to health services. The recently published positive association between diphtheria-tetanus-pertussis vaccine (DTP) and mortality (Kristensen *et al.* 2000), hardly explainable by the above-cited confounding mechanisms, has made it necessary to systematically explore the relationship between vaccines and mortality in developing countries (Fine 2000).

The present paper undertakes this exploration based on data from the Niakhar study area in Senegal, where a population follow-up has been conducted since 1983 in connection with epidemiological surveillance targeted towards vaccinations and vaccine preventable diseases.

Materials and methods

The Niakhar project, coordinated by Institut de Recherche pour le Développement (IRD, formerly ORSTOM), has been described elsewhere (Garenne & Cantrelle 1997; Delaunay *et al.* 2001). The study area, located 115 km east of Dakar, comprises 30 villages and around 30 000 persons. Village populations range from 50 to 3000 inhabitants and agriculture is virtually the sole occupation.

From September 1989 to February 1997, studies on the efficacy of vaccine against measles and pertussis were conducted in the area (Garenne *et al.* 1991; Simondon *et al.* 1997; Preziosi *et al.* 2002). During that period, weekly home-based surveys were conducted in which demographic events, including births, deaths and migrations were recorded, as well as epidemiological events, such as measles or pertussis cases and vaccinations. The project vaccinated all infants born in or migrated into the study area; hence, the vaccination status was completely accurate. The normal schedule included three doses of

DTP-poliomyelitis vaccine (DTP-IPV) at 2, 4 and 6 months of age. BCG was given with the first DTP-IPV dose. Measles vaccine (MV) was given at 9–10 months of age. Mothers were notified 1 week ahead of the scheduled vaccination session; transportation was then provided to and from the healthcare centre. With each injection, mothers were provided with anti-malarial prophylaxis (chloroquine) for the child, in quantities sufficient to cover the period until the next scheduled injection, or 3 months after the last session. Therefore, fully vaccinated children were also potentially protected against malaria up to 12–13 months of age, although whether this chloroquine was actually used as prophylaxis or kept for treatment of malaria or other fevers is not known. During this period, vaccine coverage achieved high levels: 89% for BCG and DTP and 74% for MV. It should be noted that, with few exceptions, the first dose of DTP (DTP1) and BCG were given together on the same day, so that these two vaccines could not be analysed separately.

Since March 1997, demographic surveys have been carried out at a slower pace, with one every 3 months. During that period, vaccinations were provided by the Expanded Programme on Immunization of Senegal. The schedule was the same as in the previous period, except that oral polio vaccine was given in place of IPV. Transportation was no longer provided, and vaccine coverage dropped to about 50% for BCG and DTP and 20% for MV. During that period, administration of BCG and DTP1 on the same day was less common although these vaccines are not independently distributed in the population ($\chi^2 = 581$, d.f. $= 1$, P-value $= 0$). Vaccination status was assessed retrospectively by inspection of vaccination cards by field workers during home visits. This implies that some children may have been recorded as unvaccinated while they actually had been vaccinated, if their mother was not seen at subsequent visits or if the card was lost, and also that vaccination dates are less precisely known.

In order to take into account these differences in vaccine coverage and data collection, we decided to study two cohorts independently. The first cohort included the 8277 children born in the area between 1 September 1989 and 31 August 1996. The second cohort included the 4114 children born in the area between 1 September 1996 and 31 December 1999. The limit between the two cohorts was chosen so that the last children included in the first cohort were 6 months old at the time when the survey method and the vaccination procedures changed. As BCG and DTP could not be studied independently, we decided to retain children who had received BCG and DTP1 on the same day, and those never vaccinated with BCG or DTP. This excluded 481 children (6%) from cohort 1 and 541 (13%) from cohort 2. Hence the first cohort included 7796 children and the second cohort 3573 children. Subsequent doses of DTP were ignored. Polio, yellow fever and meningitis vaccinations were also ignored.

Potential confounders included in the study were: gender, birth rank (this variable was not recorded for births occurring after February 1997), mother's age, mother's education, number of siblings, number of older siblings who had died before 2 years of age.

As this is an observational study and more prone to over-interpretation than a designed experiment, it is important to indicate here which elements of the analysis strategy were determined in advance. The decision to study survival up to the age of 2 years followed guidelines provided by the WHO Vaccine Assessment and Monitoring Division (WHO 2001). The decision not to study BCG and DTP separately resulted from having noted that there were too few children who had received only one of the two vaccines. Hence these children, as well as those having received DTP1 and BCG on different days, were excluded after a first examination of the data set.

The association between vaccines and survival was analysed through the proportional hazards models with age as the time scale. Children were included at birth and followed up to 2 years of age (or death or outmigration). Vaccine status was coded as two time-varying covariates: one for BCG/DTP and the other for MV (Therneau & Grambsch 2000).

Results

Table 1 shows the age range at vaccination. The narrow range of ages in cohort 1 reflects the very unusual and better controlled procedure used during this period, when compared with the standard EPI procedures used in cohort 2.

Table 2 shows the effects of the putative confounding factors on survival in the age interval (0–2 years), estimated by the Cox model. In two cases (birth rank in the first cohort, gender in the second cohort), a test rejected the proportionality of hazards hypothesis; hence the mortality ratio has no meaning and the corresponding estimate was

Table 1 Age (in months) at vaccination

Vaccine	10th percentile	Median	90th percentile
First cohort			
BCG/DTP1	2.3	2.8	3.6
MV	7.9	9.7	10.2
Second cohort			
BCG/DTP1	1.8	3.2	7.8
MV	8.2	10.3	16.9

Table 2 Potential confounding factors

	Mortality ratio (95% CI)	
Covariate	First cohort	Second cohort
Gender (male vs female)	1.23 (1.08–1.41)	Not computed
Mother's age (quantitative)	1.00 (0.99–1.01)	1.01 (1.00–1.03)
Number of older siblings who died before 2 years of age	1.16 (1.04–1.29)	1.23 (1.1–1.39)
Birth rank (>1 vs 1)	Not computed	Not available
Mother's education (none/primary)	0.97 (0.77–1.24)	0.65 (0.46–0.91)
Number of siblings (quantitative)	1.00 (0.98–1.02)	1.00 (0.98–1.02)

Not computed: hazards not proportional. Not available: covariate not recorded.

not computed. There are some inconsistencies between the two cohorts. Mother's age and mother's education are significantly associated with mortality in the second cohort only. However, inclusion of these covariates in the statistical models (as stratum variables when the proportionality assumption could not be made) did not alter the vaccine effect estimates; hence mortality ratios are given unadjusted.

Table 3 shows the mortality ratios for BCG/DTP and MV. BCG/DTP is associated with reduced mortality, this association being statistically significant for both cohorts. MV is not associated with mortality. The interaction between the two vaccines is not statistically significant (*P*-values 0.93 and 0.24 for cohorts 1 and 2 respectively).

In order to better understand the association between MV and mortality, we separately assessed it among recipients and non-recipients of BCG/DTP. This study was possible only for the second cohort as in the first cohort, MV and BCG/DTP are too strongly associated. The results are shown in Table 4. For this study, children were included at 1 year, with BCG/DTP and MV statuses fixed at inclusion, and were followed up to 2 years. Children emigrating or receiving vaccinations after inclusion were censored. No findings are statistically significant, but the figures suggest that MV could be associated with reduced mortality among non-BCG/DTP recipients.

Discussion

In both cohorts, we found a positive association between BCG/DTP and survival, and no association with measles vaccination. These results concern survival up to 24 months of age, but we also studied survival up to 6, 12 and 18 months of age, as well as survival in the 6–24 and 12–24 months age intervals. The results are not shown, as they are very similar to those reported. The results are quite consistent between the two cohorts. This has implications concerning two potential biases. First, it has been argued (Aaby & Jensen 2005; Jensen *et al.* 2005) that when vaccinations are recorded retrospectively, as was the case for cohort 2, a bias should result, because vaccinations of children who died before the survey are less likely to be recorded than vaccinations of children still alive at the time of the survey. Although this argument is theoretically correct, it is not easy to obtain even a rough estimate of the magnitude of this bias. In our study, it would increase the apparent protective effect of vaccines in the second cohort as data were collected by a 3-month

Table 3 Mortality ratios for BCG/DTP and measles vaccine (MV) before age 2 years

Vaccine	Follow-up	Deaths	MR (95% CI)	*P*-value
First cohort (1989–1996)				
(BCG/DTP)–	27 906 (3.6)	371	0.70 (0.50–0.97)	0.03
(BCG/DTP)+	131 364 (19.1)	494		
MV–	83 815 (10.8)	589	0.98 (0.75–1.27)	0.87
MV+	75 454 (13.6)	286		
Second cohort (1996–1999)				
(BCG/DTP)–	43 537 (12.3)	351	0.59 (0.46–0.74)	0.00000008
(BCG/DTP)+	28 862 (18.4)	116		
MV–	65 018 (18.4)	438	0.87 (0.57–1.30)	0.49
MV+	7381 (12.5)	29		

MR: mortality ratio (95% confidence interval in parentheses).
Follow-up is in persons × months, per person average in parentheses.

Table 4 Effect of measles vaccine (MV) among recipients and non-recipients of BCG/DTP from 1 to 2 years of age for the second cohort (1996–1999)

Vaccination	Sample size	Follow-up	Deaths	MR (95% CI)	*P*-value
(BCG/DTP)–					
MV–	1464	16 105 (11.0)	112	0.21 (0.03–1.47)	0.12
MV+	64	750 (11.7)	1		
(BCG/DTP)+					
MV–	1259	13 090 (10.4)	67	0.78 (0.49–1.26)	0.31
MV+	503	5750 (11.4)	23		

MR: mortality ratio (95% confidence interval in parentheses).
Follow-up is in persons × months, per person average in parentheses.

home visits. Conversely, it would not be a problem in the first cohort, in which vaccines were administered by IRD and simultaneously recorded. The consistency in mortality ratio estimates between the two cohorts suggests that the bias is minor, at least when the survey interval is 3 months.

Secondly, we do not know why some mothers choose to have their children vaccinated, while other mothers do not. It is conceivable that those mothers who take their children to vaccination sessions tend to take them to dispensaries when they are ill, thereby enhancing their survival. This effect is likely to be far less pronounced for the first cohort, where considerable efforts were made to bring every child to the vaccination centres, than in the second cohort where standard procedures were used, so that a larger protective effect of vaccines would be expected in the second cohort, if indeed this bias plays a prominent role in the observed association between vaccines and survival, as has been suggested (Fine 2005).

Despite these reassuring considerations, many other biases and confounding factors may be present (Fine 2004). For example, pertussis was extensively studied in this area, thus implying that doctors visited every home where a case was reported. Obviously, these doctors provided care to all children in the house when necessary. As pertussis cases are (negatively) associated with DTP vaccinations, and medical care is (positively) associated with survival a negative association between DTP and survival may result if vaccinations tend to be clustered in households. This kind of problem is likely to arise in all area in which long-term health monitoring have been undertaken.

Several other studies (Breiman *et al.* 2004; Vaugelade *et al.* 2004; Lehmann *et al.* 2005) also show a reduction in mortality among recipients of DTP and BCG, although the estimated mortality ratios are not in close agreement.

In contrast, a number of studies (summarized in Garly & Aaby 2003) show a reduction in mortality among measles vaccination recipients, whereas in our study, such an association is not statistically significant, although the point estimates are on the side of a slight reduction in mortality. This is not necessarily contradictory, for three reasons. First, different studies have used different age intervals and censoring schemes, and although in our study, mortality ratios are very stable with respect to age intervals, that need not be the case for other studies. Secondly, albeit studied for their 'non-specific effects', vaccines cannot be expected to protect against every pathogen or disease, and pathogen abundances and disease prevalences obviously vary in different ecosystems. Thirdly, it is not clear from that review whether in those studies other vaccines, especially BCG and DTP, were taken into account.

The association between MV and mortality among non-BCG/DTP recipients is not statistically significant, but the fivefold reduction in mortality warrants a tentative explanation, especially in view of the moderate to null reduction in mortality among BCG/DTP recipients. This difference could be explained by the existence of a protected subpopulation, be it because of a wealthier family or a more concerned mother, etc. and by the fact that vaccinations indicate membership in that group. Then, BCG/DTP-vaccinated children would presumably belong to the protected group, and a subsequent vaccination would not change their survival, whereas non-BCG/DTP recipients would include children from the unprotected group and also some children from the protected group who for some reason have missed the BCG/DTP vaccination. Vaccination with MV would thus 'reveal' their true group.

Overall, our findings are compatible with a sociological effect of vaccination on survival. Controlled experiments are necessary to settle this issue (Fine 2005) although whether this is ethically defendable may be subject to controversy. While the choice of studying all-cause mortality is understandable in developing countries, where morbidity is rarely recorded at the individual level, and where causes of death are generally not known, new insights will clearly arise from careful observation of the distribution of diseases among recipients and non-recipients of the different vaccines.

Acknowledgements

EE, FS, KS, JV, AM were funded by the Institut de Recherche pour le Développement. From 1989 to 1997, the

Niakhar Population and Health Project was mainly supported by Aventis-Pasteur, Lyon.

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