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Non-specific effects of childhood vaccinations – A case control study nested into a Health and Demographic Surveillance System in rural Burkina Faso

G. Pfeiffer [a,*], A.B. Fisker [b], E. Nebié [c], J. Hengelbrock [d], A. Sié [c], H. Becher [a,d], O. Müller [a]

[a] Institute of Public Health, Ruprecht-Karls Universität Heidelberg, Germany
[b] Research Centre for Vitamins and Vaccines, Bandim Health Project, Statens Serum Institut, Copenhagen, Denmark
[c] Centre de Recherche en Santé, Nouna, Burkina Faso
[d] University Medical Center Hamburg-Eppendorf, Department of Medical Biometry and Epidemiology, Germany

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ABSTRACT

Introduction: Previous studies in African countries have been suggestive of non-specific effects (NSE) of vaccination on child survival. Live vaccines (e.g. measles, MV) have been found to reduce child mortality while inactivated vaccines (e.g. diphtheria-tetanus-pertussis, DTP) have been associated with increased mortality; NSE were often found to be sex-specific.

Methods: A case-control study nested into the Health and Demographic Surveillance System (HDSS) cohort of the *Centre de Recherche en Santé de Nouna* (CRSN) was conducted in northwestern Burkina Faso. A total of 3,010 children born in 2009–11, were included in the study, 375 cases and 2635 age and village matched controls. The main outcome measures were the mortality odds ratios for vaccinated versus unvaccinated children by antigen. The main outcome measures were the mortality odds ratios for vaccinated versus unvaccinated children by antigen.

Results: Most deaths occurred in late infancy, and there were significantly more deaths in males as compared to females (OR 1.29, CI 1.04–1.60). Overall, there was no statistically significant association between vaccine status and mortality. However, among children in the age group 2–8 months, there was a consistent sex-differential pattern for all doses of oral polio vaccine combined with pentavalent vaccine (OPV + Penta), with the vaccines being associated with lower mortality in boys, but not in girls. Routine MV + yellow fever vaccine was associated with reduced mortality, but only before mass vaccination campaigns with meningitis and measles vaccines took place.

Conclusions: The findings of this study provide further support on the existence of NSE of childhood vaccinations in a large population of rural Burkina Faso. More randomized controlled trials are needed to confirm these observations.

1. Introduction

Vaccinations are among the most effective and cost-effective interventions in the field of public health [1,2]. In particular, the Extended Program on Immunization (EPI) of the World Health Organization (WHO) is considered a success story having averted some two million deaths per year in the recent past [3–6].

A range of epidemiological studies in low- and high income countries support the presence of non-specific effects (NSE) of vaccinations [7–11]. These are the observed effects of a vaccination on overall morbidity and mortality that cannot be explained by the specific effect of a vaccination, the prevention of the targeted infection. While the beneficial character of vaccinations on the targeted diseases is well researched and not in question, there is accumulating evidence of both beneficial [12–16] and detrimental NSE [17–19]. The understanding of NSE is growing with immunological data backing the epidemiological findings [20]. While a causal mechanism is still to be proven, it is obvious that NSE are associated with the type of vaccine administered. Live vaccines have been found to reduce child mortality, while inactivated vaccines have been found to be associated with increased child mortality [18,21–23]. Moreover, NSE are often observed to be sex differential [10,18,24].

Evidence from observational studies indicates that inactivated vaccines such as diphtheria-tetanus-pertussis (DTP), hepatitis B (HBV) and polio (IPV) vaccines are associated with increased

* Corresponding author at: Institute of Public Health, Ruprecht-Karls Universität Heidelberg, INF 324, 69120 Heidelberg, Germany.
E-mail address: Gillian.Pfeiffer@hotmail.de (G. Pfeiffer).

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overall mortality in young girls, in spite of protection against the targeted diseases [19,21,22,25,26]. In contrast, the live measles vaccine (MV), Bacille Calmette-Guerin (BCG) and oral polio vaccine (OPV) have been shown to reduce mortality [27,28]. These contrasting effects have often been observed in the same populations [29], suggesting that inactivated and live vaccines leave the immune system in very different states. The beneficial NSE of live vaccines have been confirmed in randomized controlled trials (RCT) [14,30,31].

Until today and due to ethical considerations, observational studies have remained the only available method for exploring the controversial association between inactivated vaccines already included into WHO-EPI and mortality. The present study examines the association between routine childhood vaccinations and mortality in Burkina Faso through a nested case-control study approach.

2. Methods

2.1. Study area

The study was conducted in the area of the Health and Demographic Surveillance System (HDSS) of the *Centre de Recherche en Santé de Nouna* (CRSN) [32]. In 2010, the Nouna HDSS comprised about 78,000 inhabitants residing in the town of Nouna and 58 surrounding villages. The population is served by 16 peripheral health centres (CSPS). The study area is a Sub-Sahelian dry orchard savannah with a long dry (November–May) and a short rainy (June–October) season. The population consists mainly of poor subsistence farmers, and malaria is highly endemic in the area [33].

2.2. Study design

A nested case-control study design was used to analyze the association between vaccination status and child mortality. Cases and controls were drawn from the Nouna HDSS cohort. From the total cohort of children born between 01.01.2009 and 31.12.2011, children who died between the age of 2 and 24 months were selected as cases. Controls were matched to cases by date of birth (within a year) and village of residence. We used risk-set sampling [34]. The risk-set was composed of all children to whom the matching criteria applied. After controls were matched to a case the individuals were not taken out of the risk-set, instead they remained eligible for control selection to the next case. The same individual could be selected (by chance) as a control for more than one case during the follow-up. Additionally, a control could eventually become a case. Twins of enrolled children were excluded as possible controls. Up to 10 controls were matched to each case (supplementary Table 1).

2.3. Data collection

Households of the Nouna HDSS are routinely visited every 4 months by trained field workers of the CRSN to register vital events such as births, deaths, and in- and out-migration. Each individual is given a HDSS-specific identification number. With these data, all individuals can be linked to their parents, children, and siblings. The detailed procedures are described elsewhere [32].

For the respective population, the CSPS regularly provide the possibility to be vaccinated (center-based in the CSPS villages on a daily basis and during outreach visits in the surrounding villages usually once every month). Information on vaccinations is documented in vaccination books stored at the health centers. Children are registered at the time of their first vaccination and the CSPS vaccination books are updated during each vaccination contact. For this study, information on vaccinations of the study subjects was collected using the CSPS vaccination books. Integrating CSPS routine vaccination data and HDSS follow-up data in some cases uncovered inconsistencies in record keeping between the two data sources, e.g. some vaccinations were recorded as being given before the birth or after the death of a child. In these cases the date of birth or death of the subject was changed to the most plausible date with the CSPS books used to correct the information, since the HDSS information was obtained during the 4 monthly visits and was considered to be less accurate. If inconsistencies could not be resolved easily, the respective children were excluded from the analysis. For this study, demographic and vaccination data up to July 2014 were used.

2.4. WHO-EPI vaccination schedule

Fig. 1 shows the routine WHO-EPI child vaccination schedule for Burkina Faso. It includes five different vaccines for the prevention of nine infections: (i) BCG, (ii) OPV, (iii) Pentavalent Vaccine (Penta) consisting of DTP + Haemophilus influenzae type b (HiB) + Hepatitis B (HBV), (iv) yellow fever vaccine (YF), and (v) MV.

The recommended vaccination schedule in Burkina Faso is BCG and first dose of OPV (OPV0) at birth, first dose of Penta (Penta1) and OPV1 at 8 weeks, Penta2 and OPV2 at 12 weeks, Penta3 and OPV3 at 16 weeks, and MV plus YF vaccination at 9 months (270 days) of age. In addition, children received vaccinations (in particular frequent OPV) through national vaccination campaigns (Fig. 2).

2.5. Study subjects and inclusion criteria

The inclusion criteria for cases and controls were as follows: (i) birth and if so death within the Nouna HDSS, (ii) entry in the CSPS vaccination book.

2.6. Vaccination data

The vaccination data were obtained by seeking out the child in the vaccination books at the local CSPS by name and birth date. Since children were registered in the books upon first vaccination, any child that was identified in the vaccination books had received at least one vaccination. Therefore, all children included in analysis had received at least one vaccination.

While the recommendation for Penta and OPV vaccination is 8, 12 and 16 weeks, it is in reality implemented as 2, 3 and 4 months. We conducted a sensitivity analysis using the WHO vaccination dates and found no significant differences in study results (supplementary Table 2).

Study subjects were classified as vaccinated if they had received the respective vaccination at the age of the death of the case. Children were classified as "not eligible" for a vaccination if the corresponding case died before it reached the age to be eligible for vaccination, i.e. the recommended date of vaccination. This way, all children of one risk set had the same exposure time, namely the survival time of the respective case. Vaccinations received outside of this exposure time are not considered.

2.7. Statistical analysis

The association between vaccination status and child mortality was estimated using conditional logistic regression models [35]. For each vaccination of interest (Penta 1, Penta 2, Penta 3 and MV), two separate models were estimated: in the first, the overall association of vaccination status and mortality was estimated, controlling for the effects of sex. In the second, the sex-specific associations of vaccination status and mortality are estimated by

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