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Fewer out-of-sequence vaccinations and reduction of child mortality in Northern Ghana

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ABSTRACT

Background: Studies suggest that diphtheria-tetanus-pertussis (DTP) vaccine administered simultaneously with measles vaccine (MV) or DTP administered after MV are associated with higher child mortality than having MV-after-DTP3 as most recent vaccination. We tested this in Northern Ghana where the prevalence of such out-of-sequence vaccinations has declined.
Methods: Using annual cohort data of children aged 12–23 months from 1996 to 2012 and Cox proportional hazards models, we assessed survival in relation to the most recent vaccination status within the next 12 months and until five years of age. We assessed whether mortality in children aged 12–59 months was higher when the most recent vaccine was non-live (DTP) rather than live (MV or OPV).
Results: Out-of-sequence vaccinations with DTP-containing vaccines and MV declined from 86% in 1989 to 24% in 1996 and 0.7% in 2012. Between 1996 and 2012, 38 070 children had their vaccinations status assessed: the adjusted hazard ratio (HR) for out-of-sequence vaccinations (DTP >= MV) compared with the recommended sequence of MV-after-DTP3 was 1.42(1.06–1.90) during the first 12 months after assessment of vaccination status and 1.29(1.03–1.60) with follow-up to five years of age; the HR was 2.58(1.14–5.84) before OPV or MV campaigns and 1.37(1.02–1.85) after the campaigns.
Conclusion: Out-of-sequence vaccinations with DTP and MV are associated with higher mortality than MV as most recent vaccination; the effect is unlikely to be due to confounding. Hence, the reduction in out-of-sequence vaccinations may have lowered child mortality. It is recommended not to give DTP with MV or DTP after MV.

1. Introduction

WHO's Expanded Program on Immunization (EPI) recommends whole cell diphtheria–tetanus–pertussis (DTP) to be given at 6, 10 and 14 weeks and measles vaccine (MV) at 9 months of age. However, due to weak health systems, these schedules are often not followed; many children receive DTP simultaneously with MV or after MV, i.e. out-of-sequence vaccinations.

Studies in low-income countries suggest that vaccines may have non-specific effects (NSEs) on child survival which are not explained by the prevention of the targeted infection [1–8]. These NSEs may have sex differential effects on mortality [9]. The NSEs may be due to epigenetic changes reprogramming innate immunity, as has been shown for BCG, and may change once the child gets a new vaccination [10,11]. WHO's Strategic Advisory Group of Experts on Immunization (SAGE) recently reviewed the evidence for potential NSEs of BCG, DTP and MV and recommended further research into these effects [12,13]. Live vaccines reduce mortality more than expected [1–5] but unfortunately inactivated vaccines may enhance susceptibility to unrelated infections [6–8]. Vaccines interact with each other and other immuno-modulating health interventions. Changing the sequence of vaccination may therefore lead to positive or negative NSEs. Consistent with the differential effects of live and inactivated vaccines, African and Asian studies have suggested that out-of-sequence vaccinations may be associated with higher mortality than having MV as the most recent

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vaccination [6,9,14–17]. The recent WHO Strategic Advisory Group of Expects (SAGE) on immunization review summarized 5 studies showing that DTP with MV was associated with a mortality rate ratio (MRR) of 2.30 (1.56–3.39) compared with DTP before MV, and 3 studies finding that DTP after MV was associated with a MRR of 2.16 (1.25–3.74) compared with DTP before MV [12]. Hence, elimination of out-of-sequence vaccinations could contribute importantly to lower child mortality.

The World Health Organization and other international organisations have been strategizing to improve vaccination coverage. In the region where this study was conducted, about 66% of children aged 12–23 months were fully vaccinated i.e. received BCG, three doses of DTP and polio vaccine (excluding polio0), and MV in 1996 [18]. The coverage for fully vaccinated children increased to 85% by 2012 [19]. Under-five mortality also declined from 155/1000 live births to 72/1000 live births in the same period [18,19]. Despite the improvement in vaccination coverage in low and middle income countries, vaccines are still administered out of the WHO recommended sequence in some settings [20].

In a study conducted in Navrongo, Ghana from 1989 to 1991, over 86% of children received DTP and MV out of the recommended schedule [21]. In Ghana, pentavalent (Penta) vaccine (DTP + haemophilus influenza b + hepatitis B vaccine) was introduced in January 2002 to replace DTP and is given like DTP at 6, 10 and 14 weeks. Even though the country has made significant progress in vaccination coverage, no study has examined the effect on child mortality of administering DTP/Penta and MV out-of-sequence in Ghana.

The Navrongo Health and Demographic Surveillance System (HDSS) in Northern Ghana have documented routine vaccinations of children since 1996. Vaccination data were also collected in 1989–1991 in relation to a randomised trial of vitamin A supplementation (VAS) for children aged 6 months to five years [21,22]. Using these data, we examined whether out-of-sequence vaccinations were associated with higher mortality than having received MV-after-DTP3 as the most recent vaccination. We assessed whether the effect differed in the period DTP and Penta were used, and whether the effect was affected by the many general campaigns with oral polio vaccine (OPV) or MV. Finally, we assessed how changes in out-of-sequence vaccinations could have contributed to the decline in child mortality toward Millennium Development Goal 4 (MDG4).

2. Material and methods

2.1. Study setting

The study area is the Kassena-Nankana East and West Districts of northern Ghana with an estimated population of 160,000 under continuous demographic surveillance. It covers a land area of 1675 km^2. It has one major hospital that acts as a referral hospital to seven health centers and a private clinic. There are over 40 Community Health Compounds (CHCs) that are maned by trained nurses to provide basic health care as well as provide routine vaccinations where they are located. The district is mostly rural (80%) with the primary occupation being subsistence agriculture. Socioeconomic status, maternal education and marital status are among the major determinants of child mortality in the study area [23].

2.2. Data

The study used routine vaccination data from the Navrongo HDSS which is a monitoring tool for assessing the impact of health interventions. The Navrongo HDSS has documented demographic events such as births, deaths, pregnancies and migrations 3–4 times a year since 1993. From 1996 to 2010, as part of the operations of the HDSS, we collected routine vaccination data once annually in the October-December round of data collection from health cards of children aged two years or below. From 2011 to 2012, we increased the frequency of the routine vaccination data collection by collecting vaccination data three times in a year (every four months) from children aged three years or below.

We also analyzed vaccination data collected in 1989–1991 in relation to a vitamin A trial for children aged 6 months to five years. The children were followed every 4 months for two years to distribute vitamin A supplements and to ascertain survival.

We therefore analyzed three data sets: 1996–2012 (the main analysis), 1989–1991 (the vitamin A trial), and 1996–2003 (stratified analysis during the implementation of the Community-based Health Planning and Services (CHPS) study).

2.3. Ethics approval

The study was reviewed and approved by the institutional review board of the Navrongo Health Research Centre.

2.4. Statistical methods

Data were analyzed using STATA 12.1. The analysis was limited to children aged 12–23 months on interview date. Vaccination status at enrolment was categorized into 6 groups based on the vaccines received (Table 1). Cox proportional hazards models with age as the underlying time and reported as mortality hazard ratios (HRs) with 95% confidence interval (CI) were used to assess the association between vaccinations status and subsequent mortality. The proportional hazards assumption for the Cox proportional hazard models were checked visually (supplementary Fig. 1) and tested using Schoenfeld residuals. We adjusted for age, wealth index, sex, maternal education and interview year. A wealth index was computed from household assets using principal component analysis (PCA). We assessed whether there was waning of the vaccine effect by using time-since-vaccination as the underlying time and adjusted for age using 3-month age intervals.

Mortality was assessed prospectively from the day vaccination information was collected using the landmark approach to reduce survival bias [24] and observed for 12 months of follow-up and then till they attained age five. Since the children could have received several other interventions during follow-up till five years of age (e.g. missing routine vaccinations, campaign vaccinations, and VAS campaigns), the 12 months follow-up is likely to be the best estimate of the effect of out-of-sequence vaccinations. Follow-up was censored on 30th April 2012 because rotavirus and pneumococcal vaccines were introduced in May 2012. Analysis was stratified by the periods DTP and Penta were used and by sex. Missing values were excluded from the regression models. About 2.8% and 3.1% of the children had missing values for maternal education and wealth index respectively. There was no difference in the distribution of the vaccination status of the children included and excluded from the regression model ($P = 0.25$).

To clarify how improved routine services in the villages affected MV coverage, the prevalence of out-of-sequence vaccinations and the effect of these vaccines on mortality, we examined the Community-based Health Planning and Services (CHPS) program which was tested in Navrongo In the period 1994–2003. Trained nurses, known as community health officers (CHOs), were relocated into communities to provide basic health care as well as routine vaccinations to children in the communities [20]. The intervention with CHOs had a marked effect on child survival and became the national health delivery policy in Ghana [20,21]. During the experiment, the entire district was divided into four experimental cells. Cell 1 had community health volunteers (CHVs)