EBioMedicine 8 (2016) 341–348

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Research Paper

Non-specific Effects of Vaccines and Stunting: Timing May Be Essential

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ARTICLE INFO

Article history:
Received 11 March 2016
Received in revised form 4 May 2016
Accepted 9 May 2016
Available online 12 May 2016

Keywords:
Non-specific effects
Vaccination
Stunting
Time-dependency
Policy

ABSTRACT

Background: Bacillus Calmette-Guérin (BCG) vaccination possesses effects on health beyond its target disease, the so called "non-specific effects". We evaluate these effects, as well as the effect of timing of BCG and other vaccinations, on stunting in Sub-Saharan African (SSA) children under five.
Methods: We use a Big Data design, including cross-sectional data for 368,450 children from 33 SSA countries. Logistic regression analysis is used with control factors at child, mother, household and context level.
Results: Overall, BCG vaccination did not affect stunting in SSA children (OR 1.00 [0.98–1.03]). Timing of BCG vaccination was of importance ($\beta_{time} = 0.067$ [0.061–0.073]): compared to unvaccinated children, BCG was associated with lower odds on stunting for children vaccinated early in life (OR 0.92 [0.89–0.94]) and higher odds for children vaccinated later in infancy (OR 1.64 [1.53–1.76]). Similar findings were done for diphtheria-tetanus-pertussis (DTP)1 and measles vaccination, and when hemoglobin concentration was used as outcome variable.
Conclusions: We found a general time-dependent pattern of non-specific effects of vaccination, with positive associations for vaccinations given early in life and negative associations for vaccinations given later in infancy. If confirmed in further research, our findings may provide a new perspective on the non-specific effects of vaccination.

1. Introduction

Live attenuated vaccines, such as Bacillus Calmette-Guérin (BCG), possess beneficial non-specific effects outside the scope of their target disease that have been associated with lower mortality rates (WHO, 2014a; Nankabirwa et al., 2015; Garly et al., 2003; Aaby et al., 2011). Vaccination with BCG increases immune responses and protects against unrelated pathogens (Kleinnijenhuis et al., 2012, 2014; Jensen et al., 2015; Clark et al., 1976), possibly through a combination of trained immunity, induced by epigenetic reprogramming of innate immune cells (Kleinnijenhuis et al., 2012), and heterologous T-helper (Th)1/Th17 immunity (Kleinnijenhuis et al., 2014). These general immune modulatory and antimicrobial effects of BCG may also affect stunting. Stunting reflects failure to reach linear growth potential in the early years of life and has a highly multifactorial etiology that includes nutritional factors, infectious diseases, and socio-economic factors (reviewed in Prendergast and Humphrey, 2014). Associations between several infectious diseases and stunting have been established, whereby the most profound effect is seen for diarrheal infections (Checkley et al., 2008). In addition to wasting of nutrients, infection-related inflammation could lead to stunting through down-regulation of insulin-like growth factor 1 (IGF-1) expression (Prendergast et al., 2014).

Stunting affects approximately 165 million children under five, many of whom live in Africa (36.5%) (Black et al., 2013) where stunting rates in many areas are over 40% (Global Data Lab, 2016). Besides being associated with an increased mortality, stunting has negative long-term effects on cognitive and psychosocial development (Crookston et al., 2011), school performance (Martorell et al., 2010), and economic productivity (Hoddinott et al., 2008). It is therefore an important outcome to establish the total impact of non-specific effects of vaccination on health status. Recently, the World Health Organization (WHO) has made a 40% reduction of stunting in children under five before 2025 a global target, underlining its importance (WHO, 2014b).

The beneficial non-specific effects of BCG suggest that this vaccine may be used to reduce stunting in low- and middle-income countries. If BCG vaccination indeed reduces stunting, there would be substantial potential for improvement, as coverage of BCG vaccination has stalled at 77–85% in Africa since 2009 (WHO, 2014c). Apart from vaccination coverage, timing of vaccination may be important, as the child's immune function changes with age (Kollmann et al., 2012) and early immunization had stronger consequences related to non-specific effects in one study (Aaby et al., 2011). This is important knowing that timing of vaccinations still differs widely between and within low- and middle-income countries (Clark and Sanderson, 2009).

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http://dx.doi.org/10.1016/j.ebiom.2016.05.010

We aim to study the overall effect of BCG and other vaccinations on stunting, as well as the role of timing of vaccination, on a newly developed database including data on 368,450 children under five living in 33 Sub-Saharan African countries. Given the significant variation in coverage and timing of vaccination in the daily setting in Sub-Saharan Africa, our data make it possible to study the overall effect, as well as the effect of the timing of vaccination in a much broader setting than in earlier research. To gain insight into the scope of our findings, we repeated our analyses for other vaccinations (diphtheria-tetanus-pertussis [DTP] and measles vaccine [MV]) and for another outcome (hemoglobin concentration).

2. Methods

2.1. Study Population

This study used retrospective and cross-sectional data from the Demographic and Health Surveys (DHS). DHS household surveys have been conducted in many low-income countries since the 1980s, collecting demographic, health, and nutritional indicators (www.dhsprogram.org). Each DHS consists of a household survey and separate women's and men's surveys. In the women's survey, all usual resident women aged 15 to 49 are invited for an oral interview which includes a complete birth history with detailed questions, including retrospective vaccination and stunting information, on the children born in the last five years. The team executing the DHS ensures protection of human subjects in agreement with local and international laws.

A combined dataset was derived from the Database Developing World (DDW, www.globaldatalab.org) that included all available DHS (n = 76) for Sub-Saharan African countries (n = 33) between 1998 and 2014 that included BCG vaccination and height-for-age measurement. Included were all children aged 1–60 months for whom valid information was available on stunting and BCG vaccination before age 12 months. Children aged one month or less were excluded, because of the difficulty of differentiating between stunting and fetal growth failure and of interpreting the effect of vaccination. The cut-off at 12 months for BCG vaccination was based on the importance of children being vaccinated before this point in life. There were 419,167 children aged 1–60 months in the data, of whom 50,717 were excluded because no information on stunting or BCG vaccination was available. The final study population, therefore, consisted of 368,450 children. To obtain national representative samples, the data were adjusted according to weights provided by DHS. These weights were recoded to a mean of one for all analyses performed, so that their application did not increase the sample size.

2.2. Core Measures

BCG vaccination was retrieved from vaccination cards upon visit. This was done for 183,476 of the 368,450 children (49.8%). For the 184,974 children (50.2%) of whom no card was available or vaccination was not recorded, the mother was asked whether the child was vaccinated. Timing of vaccination was calculated by subtracting the date of birth from the date of vaccination. The analysis of timing of vaccination was restricted to 171,075 children (46.4%) with valid dates on a vaccination card.

To obtain information on stunting, length or height was measured in centimeters to a precision of 1 decimal with a Shorr measuring board following a standardized DHS protocol (ICF/DHS, 2012). The measurement was voluntary and was not performed when the parent refused or the child was too sick. The assignment of anthropometric z-scores was performed by the DHS program (Rutstein and Rojas, 2006) based on the WHO Child Growth Standards (WHO. Multicentre Growth Reference Study Group, 2006). Children with scores ≤−2 were considered stunted.

We performed additional analyses using hemoglobin concentration as outcome measure. This was measured in 47 of the 76 DHS surveys, which resulted in a study population of 149,868 children aged 6–60 months. This age range differs from that for stunting, since fetal hemoglobin is usually replaced by adult hemoglobin at the age of 6 months. To measure hemoglobin concentration, the blood of the children was obtained through a finger or heel prick. Consent to draw a droplet of blood was asked after reading a consent statement to the parent or responsible adult. Obtained blood was collected in a micro-cuvette and analyzed with a battery operated portable Hemocue analyzer. Hemoglobin concentration was measured in g/dL with a precision of 1 decimal (ICF/DHS, 2012). To exclude outliers and input errors, the lowest and highest 0.1% of the hemoglobin concentrations were excluded from the analyses.

2.3. Important Covariates

We included covariates at the level of the child, the mother, the household, and the context. Inclusion of covariates was based on literature, expert opinion and availability in DHS data. Child characteristics included age (in months), sex, other vaccinations, birth order, preceding birth interval, twin status (singleton or multiple birth), size at birth (very small, smaller than average, average, larger than average, very large), and vitamin A supplementation (Benn et al., 2010; Varela-Silva et al., 2009). Age of the child was supplemented with age squared to control for non-linearity in the relationship between age and stunting. Characteristics of the mother were age (in years), height z-scores, body mass index (BMI, in kg/m^2), breastfeeding for 24 months, place of delivery (home, public hospital, private hospital, other), education (highest level), and marital status (married or living together, widowed, divorced or not living together) (Corsi et al., 2016). At the household level, the place of residence (rural, urban) and household wealth were included. Household wealth was measured by the International Wealth Index, a cross-nationally comparable index, running from 0 to 100, based on the household's possession of consumer durables (TV, fridge, car etc.), housing characteristics and access to basic services (Smits and Steendijk, 2015). Geographical information regarding sub-national district level was used to control for differences in context in which the households were living. Within the 33 countries, 285 districts were distinguished. To address missing values in the covariates, the dummy variable adjustment procedure was used (Allison, 2001). There were no missing values in the core measures.

2.4. Statistical Analysis

To determine the effects of vaccination on stunting, logistic regression analysis was performed. For the analysis with hemoglobin concentrations as dependent variable, linear regression was used. All analyses were controlled for the abovementioned covariates at the level of the child, the mother, and the household. The analysis of timing of vaccination was performed for each vaccination separately, but included controls for vaccination status with regard to the other vaccinations. To control for variation in the context in which the children lived, a fixed effects design (Wooldridge, 2013) was used for all regression models, whereby dummy variables for the 285 sub-national regions and for the survey years were included. In this way, all (measured and unmeasured) context factors related to stunting at the regional level are controlled for.

The effect of timing of BCG vaccination was studied with both a continuous and a categorical variable. The categorical time variable consisted of the categories “before 1 month”, “months 1–2.99”, “months 3–4.99”, “months 5–6.99”, “months 7–11.99”, “time unknown”, and “not vaccinated” (reference). Because MV is usually given at 9 months of age, there were few cases of MV in the early time frame. We therefore increased the upper age limit for this analysis to 15 months and chose the categories for MV as “before 6 months”, “months 6–7.99”, “months