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Timeliness of infant vaccination and factors related with delay in Flanders, Belgium

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ABSTRACT

Achieving high vaccination coverage is a necessary, but not a sufficient indicator of the quality of a vaccination programme, in terms of control and prevention of childhood infectious diseases. For optimal protection of infants, timeliness of vaccination is increasingly recognized as another important target.

The aim of this study was to assess the timeliness of measles-mumps-rubella (MMR) and diphtheria-tetanus-pertussis (DTP) vaccination in infants in Flanders (Belgium), and to identify predictors of vaccination delay. The timeliness was assessed using the Kaplan–Meier estimator in three consecutive vaccination coverage surveys among children aged 18–24 months, conducted in 2005, 2008 and 2012, respectively. Factors associated with delayed administration of the vaccines were identified using Cox regression analysis.

Over the time period, vaccination coverage for the first dose of MMR ranged from 94.0 to 96.6% and for the third dose of DTP from 97.9 to 98.7%. However, up to 32% (for MMR1) and 95% (for DTP3) of infants received vaccine doses delayed according to the recommended schedule. Although some improvement was achieved over the last decade, further efforts are needed to reach risk groups with delays, more specifically children vaccinated outside the baby well clinics, born from a mother originating from outside the European Union, children with a higher ranking or in families with a lower income.

1. Introduction

To achieve effective control of vaccine-preventable infectious diseases, a high coverage with efficacious vaccines is a prerequisite. The global target of the World Health Organization (WHO) for the vaccination coverage in infants is 90% [1]. For the elimination of measles and rubella, which is an additional goal in the American and European WHO regions, an even higher coverage is required [2].

In addition to obtaining high coverage, timely vaccination is of critical importance for reducing disease risk. Delayed infant vaccination enlarges the gap between loss of protection from maternal antibodies and full protection from vaccine-induced immunity, negatively affects herd immunity and postpones full protection in infants and children. As a consequence, infants are longer vulnerable to vaccine preventable diseases, such as Bordetella pertussis and measles, contributing to outbreaks of the latter in various countries [3,4].

Vaccination coverage is the most frequently used indicator for the evaluation and monitoring of vaccination programmes. However, age-specific infant vaccination coverage, e.g. at the age of 18–24 months, provides no information on possible delays of vaccine-administration. Timely vaccination can be assessed from cross-sectional survey data through a time-to-event analysis using the Kaplan–Meier estimator [5–8].

Recommendations on the Belgian infant immunisation schedule are published by the national Superior Health Council (SHC) [9]. In Flanders, the northern region of Belgium which represents about 60% of the population, surveys repeatedly showed high coverage estimates for vaccines recommended in infancy. In 2012, coverage rates were ≥92% for all infant vaccinations, and above 95% for the first dose of measles-mumps-rubella vaccine (MMR1) [10]. Infant vaccines are mostly administered at well baby clinics (under-5

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clinics) (83.7% of vaccines in 2012), or by a family physician or paediatrician (15.6%).

The current study focuses on adherence to age recommendations for infant vaccination against measles and pertussis, since both diseases have caused infant cases in Flanders recently, despite high vaccination coverage [11–13]. The study also aimed to detect trends over 3 coverage studies in the past 7 years, and to identify subpopulations of infants who are at higher risk for delayed vaccination.

2. Methods

2.1. Study population and survey design

The present study is based on data from three cross-sectional EPI-surveys, conducted in 2005, 2008 and 2012 in Flanders [10,14,15]. Each survey used the same study design. Infants 18–24 months of age were selected with a two-stage random cluster design. First, 125 clusters (municipalities) spread over the 5 provinces in Flanders were randomly selected with proportionate probability to their size. In each cluster, the requested number of children were then randomly selected from the National register of residents. Sample sizes were calculated based on the latest available coverage rates for each study, considering a design effect of 1.5 (2008, 2012)–2 (2005), a margin error of the confidence interval of 2.5% and a drop-out rate of 10%. The number of participants was 1354 in 2005 (participation rate 92.2%), 915 in 2008 (91.3%) and 874 (92.4%) in 2012.

The design and methods of these studies have been described in detail elsewhere [10,14,15]. In summary, parents or caregivers were visited at home by a professional interviewer, trained on the questionnaire and interpretation of vaccination data by the researchers.

Immunisation dates were transcribed from vaccination cards and completed or validated through Vaccinnet, the electronic vaccine ordering and registration system set up in Flanders in 2006 (for the 2008 and 2012 surveys) [16]. Further missing data were completed with information in medical files, as far as they could be consulted. Demographical data (age of the child, gender, rank within the family and number of siblings, number of past illness episodes) and socio-economic characteristics of the parents (family income, single parentage, parental age, employment status, educational level and ethnicity) were collected through a structured interview. The main vaccinating physician (well baby clinic, paediatrician, family physician) was defined as the one who had administered the majority of vaccine doses. Each survey was approved by the respective ethics committees of all universities involved and by the privacy commission of the Belgian Government. Written informed consent was obtained from a parent or legal guardian of each infant included in the study.

2.2. Outcome measures

In a first analysis, vaccinated children were classified by the level of delay in vaccination for MMR1 and the three doses of diphtheria-tetanus-pertussis (DTP1, DTP2, DTP3), according to the schedule recommended by the SHC. The recommended age of vaccination for MMR1 in Belgium is 12 months of age, and DTP doses are recommended at 8, 12 and 16 weeks (2, 3 and 4 months in 2005).

Time-to-event analysis was used to further analyse the age at administration and risk factors for delayed vaccination for the vaccines studied.

First, a Kaplan–Meier survival analysis was applied to the 2005, 2008 and 2012 surveys to estimate the age-specific coverage rates and 95% confidence intervals with censoring of children who had not yet received the respective dose at the time of the interview (for 2005, the start of the study was used because the interview date was not registered) [6]. The response of interest was time to vaccination, which was calculated in weeks. Timely vaccination was defined as occurring within 6 days of the recommended age for DTP and 30 days for MMR1.

In a second step, risk factors for delayed vaccination were identified using a Cox proportional hazard (PH) regression model. We opted to use continuous time-to-event analysis and not to categorize delay of vaccination, since categorizing would impact on the associations and up to now there is insufficient evidence to state which level of delay impairs vaccine effectiveness. The hazard expresses the rate for a child to be vaccinated at a specific moment in time. Reciprocal hazard ratio (1/HR) was used to present a higher risk to be vaccinated at a later age compared to the reference group (if HR > 1). Cox PH regression models used the socio-demographic variables from the interview as possible predictors. To avoid co-linearity for parental characteristics, only maternal factors were included in the analysis (except when only information on the father was available).

2.3. Statistical analysis

Cluster effects arising from the sample design were controlled for using the method developed by Ying and Wei [17,18]. The validity of the proportional hazard assumption, which is a condition for Cox regression analysis, was evaluated using Schoenfeld residuals [19]. Variables were omitted by backward stepwise selection, based on significance level (p-value > 0.1). Associations were considered statistically significant if the p-value was <0.05. Kaplan–Meier analysis was performed using SPSS 20.0 and R 2.15.1 was used for the Cox regression analysis.

3. Results

3.1. Timeliness of vaccination

Respectively 62%, 69% and 72% of infants received MMR1 before the age of 13 months (56 weeks) in 2005, 2008 and 2012 (Table 1). The largest reduction in delay over the 7 years study period was observed for doses administered more than 2 months after the recommended age.

Recommendations for administration of pertussis containing vaccines (DTP) are less well followed. The majority of children were vaccinated with a delay of 1–4 weeks, and the delay increases for subsequent doses, up to more than 2 months for 10% of DTP3 vaccinations. However, the proportion of timely administered doses also increases over the study period, especially for DTP1.

3.2. Coverage by age from Kaplan–Meier analysis

Estimates of vaccination coverage by age (inverse survival curves) were plotted in Fig. 1. The curves for DTP1 and DTP2 were similar to those for DTP3 and are not presented.

An MMR1 coverage of 95% was reached at 99 weeks of age in 2005, 77 weeks in 2008 and 75 weeks in 2012. The 2008 and 2012 plots show a higher maximum and a more outspoken rectangular shape compared to the 2005 graph, which reflects a higher adherence to age recommendations.

Coverage by age for DTP3 reached 95% at 38, 32 and 30 weeks of age in the consecutive studies. A small improvement in adherence to age recommendations for DTP3 vaccination is observed between 2005 and 2008, but not anymore from 2008 to 2012.