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Impact of infant pneumococcal conjugate vaccination on community acquired pneumonia hospitalization in all ages in the Netherlands

A.M.M. van Deursen [a,b,c,1], T.M. Schurink-van't Klooster [d,1], W.H. Man [a,c], J. van de Kassteele [e], A.B. van Gageldonk-Lafeber [d], P.C.J.L. Bruijning-Verhagen [b,d], H.E. de Melker [d], E.A.M. Sanders [a,d], M.J. Knol [d,*]

[a] Department of Pediatric Immunology and Infectious Diseases, Wilhelmina Children's Hospital, University Medical Centre Utrecht, The Netherlands
[b] Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, The Netherlands
[c] Research Centre Spaarne Gasthuis Academy, Hoofddorp, The Netherlands
[d] Department of Epidemiology and Surveillance, Centre for Infectious Disease Control, National Institute for Public Health and the Environment, The Netherlands
[e] Department of Statistics, Informatics and Mathematical Modelling, National Institute for Public Health and the Environment, The Netherlands

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ABSTRACT

Background: The long-term impact of pneumococcal conjugate vaccines on pneumonia hospitalizations in all age-groups varies between countries. In the Netherlands, the 7-valent pneumococcal conjugate vaccine (PCV7) was implemented for newborns in 2006 and replaced by PCV10 in 2011. We assessed the impact of PCVs on community-acquired pneumonia (CAP) hospitalization rates in all age-groups.
Methods: A time series analysis using Poisson regression was performed on 155,994 CAP hospitalizations. Hospitalization rates were calculated using the total number of hospitalizations as denominator. The time trend in the pre-PCV period (1999–2006) was extrapolated to predict the hospitalization rate in the post-PCV period (2006–2014) if PCV had not been implemented. Rate ratios over time were calculated by comparing observed and predicted time trends.
Results: In children <5 years of age, the observed hospitalization rates during the post-PCV period were significantly lower than predicted if PCV had not been implemented (0–6 months: 0.62, 95% CI: 0.41–0.96; 6 months – 1 year: 0.67, 95% CI: 0.50–0.90; 2–4 years: 0.78, 95% CI: 0.61–0.97). In all other age-groups, rate ratios declined over time but did not reach statistical significance.
Conclusions: After introduction of PCV, CAP hospitalizations declined in young children but no clear impact of PCV on CAP hospitalizations was seen in other age-groups.

1. Introduction

Pneumonia remains a major cause of morbidity and mortality in all age-groups with highest incidence rates in young children and older adults [1,2]. Although pneumonia is caused by several pathogens, *Streptococcus pneumoniae* remains a significant cause of community-acquired pneumonia, accounting for up to 40% or more of all cases, depending on many factors like age, geographic region, and diagnostics [3–5].

In 2000, the first 7-valent pneumococcal conjugate vaccine (Prevenar™, PCV7) was introduced for children in the United States (US) [6]. It is now part of national infant immunization programs (NIP) in numerous countries all over the world. In the Netherlands, PCV7 was included in the NIP in 2006. In 2011, PCV7 was replaced by PCV10 (Synflorix™) [7].

The implementation of PCV7 for infants dramatically reduced the incidence of vaccine-type (VT) invasive pneumococcal disease (IPD) in children [8,9]. Through herd protection it also reduced VT-IPD in all other age-groups, usually starting 1–2 years after implementation depending on local epidemiology and coverage in children [8,10]. While it is estimated that 90% of the PCV7-serotypes have disappeared 9 years after PCV7 introduction [11], non-VT (NVT) disease gradually erodes the net benefit [8,12]. In response, more-valent vaccines such as PCV10 including serotypes 1, 5 and 7F and PCV13 with extra serotypes 3, 6A and 19A were introduced leading to a further decline in IPD in the first years after introduction [13,14]. However, the net impact on overall IPD is limited by an ongoing increase in NVT-IPD, in particular in adults over 50 years of age [8,15].

In contrast to IPD, data on impact of PCVs against all-cause pneumonia is less consistent between countries [16–18]. Until

* Corresponding author at:
E-mail addresses: a.m.m.vandeursen@umcutrecht.nl (A.M.M. van Deursen), mirjam.knol@rivm.nl (M.J. Knol).
[1] Both authors contributed equally to this article.

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the mid-2000s, before the introduction of PCVs, an increasing trend in pneumonia hospitalizations was seen in both the US [19] and Europe [20,21] including the Netherlands [22]. After PCVs were introduced, a sustained beneficial effect on all-cause pneumonia hospitalizations was seen in vaccinated children under two years of age, though reductions in observational studies range between 13% and 65% [23–27], while reductions in randomized controlled trials vary between 7 and 30% depending on solely clinical or radiographically confirmed pneumonia [23,28–31]. For older age-groups, data are highly diverse [18,32,26,33,34]. This is especially the case for older adults, with a reduction of pneumonia hospitalizations in the US [17] whereas an increase in all-cause pneumonia in older adults was observed in Europe [16,18,34].

We assessed all cause pneumonia hospitalization in the Netherlands over time, both before and after the introduction of PCV7 in 2006 and PCV10 in 2011. In view of the trends in time with varying hospitalization rates for pneumonia in other countries, we conducted a population-based retrospective study over a period of 16 years (from 1999 to 2014) on all-cause community-acquired pneumonia (CAP) hospitalizations in all ages. The impact of introduction of PCV was assessed using time series analysis.

2. Methods

2.1. Pneumococcal vaccination in the Netherlands

PCV7 was introduced into the Dutch NIP in June 2006 and recommended for all infants born on or after April 1st 2006 as a 3 + 1 dose series at 2, 3 and 4 months of age with a booster at 11 months [35] without a catch-up campaign. Vaccine uptake of the complete series was around 94% in the year of introduction and remained stable in the following years [36]. In 2011, PCV7 was replaced by PCV10 for children born on or after March 1st 2011 [7]. In November 2013, the vaccination schedule was reduced from four to three doses of PCV10, given at 2, 4 and 11 months of age [7]. The 23-valent pneumococcal polysaccharide vaccine (PPV23) is only advised in specific risk groups (e.g. people suffering from asplenia, sickle-cell anemia or cerebrospinal fluid leakage), resulting in <1% of elderly having received PPV23 [37]. Overall, Dutch antibiotic consumption and prescription rates are low resulting in low antibiotic resistance rates (around 1.3% for penicillin) [38].

2.2. Surveillance data

Hospitalization data from 1999 to 2014 were retrospectively collected from the Dutch National Medical Registration database. This database collects all inpatient primary and secondary discharge diagnoses coded according to the 9th International Classification of Diseases (ICD-9) up to 2012 in the Netherlands (17 million inhabitants), and according to the ICD-10 from 2013 onwards. National data coverage was around 99% until mid-2005, but thereafter fluctuated around 90% due to changes in funding. Therefore, only data from those hospitals that provided data for the entire study period from 1999 to 2014 were used, representing 38% of the total number of hospitalizations. The provided registry data were fully anonymized and therefore approval of an ethics committee was not required.

The primary outcome CAP hospitalization was defined as (1) a primary discharge diagnosis of all-cause pneumonia or (2) meningitis, septicemia or empyema as primary discharge diagnosis and pneumonia as secondary (see supplementary Table 1 in the appendix for the selected ICD-9 and ICD-10 codes). Readmissions for pneumonia within 90 days were considered the same episode and were not included in the analyses.

2.3. Statistical analyses

Hospitalization rates attributed to CAP were calculated per month and stratified by age-group, i.e. 0–6 months, 6 months-1 year, 2–4 years, 5–17 years, 18–49 years, 50–59 years, 60–69 years, 70–79 years and 80 years or older. As population data was unavailable, the total number of hospitalizations in the respective age-group was used as a denominator. The period January 1999 to June 2006 was defined as pre-PCV period and July 2006 to December 2014 as post-PCV period. For each age-group, a Poisson model was fitted to the time series. Each time series was decomposed in a long-term time trend, a seasonal component (taking month as categorical variable), and an autoregression term to account for autocorrelation. To quantify the impact of PCV introduction, the time trend in the pre-PCV period was assumed linear and the time trend in the post-PCV period was modeled as a natural cubic spline with two degrees of freedom. The spline allowed a more flexible trend after introduction of PCV. For example, in the younger age-groups effects may be expected quickly, while in older age-groups herd effects may only be expected after a certain period. Subsequently, the linear time trend in the pre-PCV period was extrapolated to predict the hospitalization rate in the post-PCV period if PCV had not been implemented. CAP hospitalization rate ratios (RRs) were calculated in the post-PCV period by comparing the observed time trend after introduction of PCV with the predicted linear time trend. A single RR was calculated per age-group for the overall post-PCV period and RRs per age-group were calculated over time. Because Poisson time series models with an autoregressive term are not implemented in standard software, the model was reformulated in the Bayesian framework and fitted using INLA [39] in the R software environment (version 3.3.3). Confidence intervals (CIs) were obtained by simulation from the joint posterior distributions.

3. Results

Between January 1999 and June 2014, we identified 155,994 CAP hospitalizations. Patients with a primary discharge diagnosis for CAP accounted for 98.4% of these hospitalizations. The monthly CAP hospitalization rates were highest in children aged 6 months to 1 year of age and adults of 80 years and older (Fig. 1).

3.1. Time series analyses

In all age-groups the hospitalization RR decreased over time after PCV introduction in 2006 (Fig. 2). The RR compares the observed time trend in the post-PCV period with the predicted time trend if PCVs had not been implemented. In children 6 months-1 year, 2–4 years and 5–17 years the decline in RR started quickly after PCV introduction. In children 0–6 months and adults, the RR stayed around 1.0 during the first years after PCV introduction and decreased afterwards.

In children aged 0–6 months, the RR was significant from 2012 onwards resulting in an overall post-PCV RR of 0.62 (95% CI: 0.41–0.96) and a RR of 0.19 (95%CI: 0.09–0.38) at the end of the study period in December 2014. In children aged 6 months-1 year, the RR was statistically significant directly after the introduction of PCV reaching an overall post-PCV RR of 0.67, 95% CI: 0.50–0.90 and a RR of 0.47 (95%CI: 0.29–0.77) in December 2014. In children aged 2–4 years, the upper limit of the 95% CI around the RR was approximately 1.0 during the whole study period, showing borderline significance, with an overall post-PCV RR of 0.78, 95% CI: 0.61–0.97) and a RR of 0.71 (95%CI: 0.47–1.05) in December 2014.

In the other age-groups, the overall post-PCV hospitalization RR did not reach statistical significance (5–17 years: 0.88, 95% CI:

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