Does pneumococcal conjugate vaccination affect onset and risk of first acute otitis media and recurrences? A primary care-based cohort study

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ABSTRACT

Background: It has been hypothesized that widespread implementation of pneumococcal conjugate vaccination (PCV) in infancy reduces early AOM and thereby prevents further AOM episodes and associated health care resource use.

Methods: We tested this hypothesis by applying an extension of the original Cox proportional hazards model (Prentice, Williams and Petersons' total time) to individual AOM episodes recorded in pseudonymised primary care electronic health records of 18,237 Dutch children born between 2004 and 2015. Children were assigned to three groups: no-PCV (January 2004-March 2006), PCV7 (April 2006-February 2011) and PCV10 (March 2011-February 2015).

Results: Of the 18,237 newborns, 6,967 (38%) experienced at least one GP-diagnosed AOM episode up to the age of four years (median age at first AOM: 12 months, interquartile range: 12; total number of AOM episodes: 14,689). Time-to-first AOM was longest in the PCV10 group compared with the PCV7 and no-PCV groups (log rank test: $P<0.001$); in these groups 30% had experienced a first AOM at 20, 17 and 15 months, respectively. Children in the PCV10 group had a 21% lower risk of experiencing a first AOM episode than those in the no-PCV group (hazard ratio (HR): 0.79, 95% confidence interval (CI): 0.72 to 0.86), while the effect was less pronounced for the PCV7 group (HR: 0.94, 95% CI: 0.87 to 1.02). Neither PCV7 nor PCV10 reduced the risk of AOM recurrences. Compared to no-PCV, HRs for overall AOM were 1.00 (95% CI: 0.95 to 1.06) and 0.89 (95% CI: 0.84 to 0.95) for PCV7 and PCV10, respectively.

Conclusion: Our cohort study suggests that PCV postpones the onset and reduces the risk of first AOM without affecting recurrences. The impact of PCV on overall AOM in children up to the age of four years seems therefore largely attributable to the prevention of a first AOM episode.

INTRODUCTION

It has been shown that children who experience a first acute otitis media (AOM) episode in early life have a higher risk of developing multiple AOM recurrences, persistent otitis media with effusion and have higher associated health care resource use [1-4]. These first AOM episodes are often caused by *Streptococcus pneumonia*. On contrary, AOM recurrences are often caused by other otopathogens, such as *Haemophilus influenzae* [5]. Randomised controlled trials (RCTs) have shown that pneumococcal conjugate vaccination (PCV) when given during infancy can prevent pneumococcal AOM [6]. However, when given later in life, in particular in children with a history of AOM, PCV does not prevent AOM episodes [6]. This has led to the hypothesis that by preventing early AOM and thereby halting the pathogenic pathway of middle-ear mucosal damage and bacterial biofilm formation, the widespread use of PCV in infancy prevents AOM recurrences and associated health care resource use [5,7].

We tested this hypothesis by studying the impact of subsequent introduction of 7-valent PCV (PCV7) and 10-valent PCV (PCV10) in Dutch infants on AOM onset and risk of first AOM and recurrences up to the age of four years using individual primary care electronic health records over the years 2004 to 2015.

MATERIALS AND METHODS

Study Population and Data Sources

A total of 18,237 Dutch children born between January 2004 and February 2015 were included and followed during their first four years of life. These children were registered within the first six months of life at primary practices in The Netherlands that provide pseudonymised electronic health record data to two large registries: Julius General Practitioners' Network (JGPN) [8] and Zorggroep Almere (ZGA) [9]. Median follow-up was 48 months (interquartile range (IQR): 23 months). The dataset was obtained after approval by the independent scientific committees of JGPN [project number: 2017 02] and ZGA [meeting number: 28 04].

Outcome and exposure variables

From the electronic health records, general practitioner (GP)-diagnoses of AOM (International Classification of Primary Care [ICPC] code H71) were extracted. A new AOM episode was counted if there was no AOM-related GP visit for 28 days. PCV7 (Prevenar®, Pfizer) was introduced in the Dutch National Immunisation Program (NIP) in 2006, for all children born from April that year. The NIP switched from PCV7 to PCV10 (Synflorix®, GlaxoSmithKline) in 2011 for children born from March that year. PCV7 and PCV10 were initially given at ages 2, 3, 4 and 11 months. From November 28, 2013 a 3-dose schedule at ages 2, 4 and 11 months was introduced. Children in the registries were assigned to either of three groups according to their date of birth: no-PCV (January 2004 to March 2006), PCV7 (April 2006 to February 2011) and PCV10 (March 2011 to December 2015). Since its introduction in 2006, vaccination coverage has been stable and high at 93.6% to 95.1% over the entire study period [10].

Statistical Analysis

The effect of PCV (no-PCV, PCV7 or PCV10) on onset of AOM (in months) was evaluated by means of Kaplan-Meier survival analysis and by evaluating the time (in months) at which 10%, 20% or 30% of children had experienced a first AOM episode [11]. Differences in survival curves were assessed using a log rank test. To discriminate the effect of vaccination (no-PCV, PCV7, PCV10 groups), pairwise comparisons using a pairwise log rank test were performed.

To calculate AOM episode-specific hazard ratios (HRs) per PCV-group, an extension of the original Cox proportional hazards model with vaccination status (no-PCV, PCV7 or PCV10) as exposure variable was used (Prentice, Williams and Petersons' total time model (PWP-TT)). The PWP-model orders multiple episodes by stratification, based on the prior number of episodes during the follow-up period. All children are at risk for the first episode, but contributions to the *k*-th risk set is restricted to those children who have experienced ($k - 1$) episodes and thus, for the analyses on second, third, etc. episodes, children *not* experiencing a first episode were *not* included [12,13]. For this model, time-to-event was defined as the number of days between start of follow-up (t=0 being the date of birth) and censor date. The censor date was defined as either: date of (first or *k*-th) AOM; date at which the child became four years old; date of drop-out from the primary care registry; or end of follow-up (December 31, 2015), whichever came first. With 95% of children having fewer than five AOM episodes, episodes beyond the fifth (n=688 out of n=14,689 episodes available in the dataset) were not used for the analyses of AOM recurrences as this could make the model unstable [12]. We further estimated the impact of PCV on the risk of overall AOM episodes during the study observation period by including all AOM episodes (n=14,689). The antilogs (exponentiation) of the coefficients from the models were taken to calculate HRs and its corresponding 95% confidence intervals (CIs). The proportionality assumption was checked using scaled Schoenfeld residuals and nonlinearity using lognegative-log. Analyses were performed in RStudio, Version 1.0.136 (2016).

RESULTS

Of the 18,237 newborns, 38% (*n*=6,967) experienced a first GP-diagnosed AOM episode (median age: 12 months (interquartile range (IQR: 12 months)). Of those 3,585 (52%) had one or more AOM recurrences (total number of recurrences: 7,722). The proportion of children experiencing one or more AOM episodes was 47.2% for no-PCV, 46.4% for PCV7 and 25.1% for PCV10, respectively (Figure 1a). Figure 1b illustrates the distribution of AOM episodes among children who experienced at least one AOM episode per group.

Children in the PCV10 group had a 21% lower risk of experiencing a first AOM episode in their first four years of life than those in the no-PCV group (HR: 0.79, 95% CI: 0.70 to 0.89), while the effect of PCV7 was less pronounced (HR: 0.94, 95% CI: 0.84 to 1.05).

Time-to-first AOM was longest in the PCV10 group compared with the PCV7 and no-PCV groups as illustrated by the Kaplan-Meier curves (Figure 2, log rank test $P<0.001$; pairwise comparisons, PCV7 versus no-PCV: $P=0.13$, PCV10 versus no-PCV: $P<0.001$). In these groups, 30% had experienced a first AOM at 20, 17 and 15 months, respectively (Table 1). However, neither PCV7 nor PCV10 reduced the risk for subsequent AOM episodes (Table 2). Compared to no-PCV, HRs for overall AOM were 1.00 (95% CI: 0.95 to 1.06) and 0.89 (95% CI: 0.84 to 0.95) for PCV7 and PCV10, respectively.

DISCUSSIONS

Our observational study supports the hypothesis that widespread use of PCV prevents early AOM [5]: using a large dataset of routinely collected electronic primary care data we show that PCV, and particular PCV10, postpones the onset and reduces the risk of first AOM. However, we found no effect of PCV on AOM recurrences up to the age of four years, suggesting that the impact of PCV on overall AOM is largely attributable to the prevention a first AOM episode.

A recent primary care-based cohort study from Iceland found large reduction of overall AOM (HR 0.78, 95% CI 0.69 to 0.88) by PCV10 which was mediated by the prevention of the first two AOM episodes [14]. The Icelandic authors, had applied the Anderson-Gill (AG) extension of the Cox regression model. To explore whether the type of regression model used, contributed to the difference in the magnitude of the effect size of PCV10 on overall AOM between the studies (HR 0.89 versus HR 0.78), we reran our analysis using the AG model; this showed a HR of 0.81 (95% CI 0.76 to 0.87) which is very similar to that reported by Sigurdsson S, *et al*. [14]. The differences in effects observed between the PWP-TT, which is also referred to as a stratified AG model [13], and AG models illustrates that any reported effects of PCV on overall AOM episodes should be interpreted with caution. For this, one should take into account that the AG model assumes that the risk of recurrent events is constant regardless of the number of previous events [12]. However, when the occurrence of a previous event increases the likelihood of further episodes, which is likely to be the case for AOM, then PWP is recommended [12,13].

Our observations are consistent with the post-hoc analyses of the Finnish OM trial showing that PCV7 had little effect on subsequent AOM episodes in children below 2 years of age [15]. Jokinen, *et al*. reported that PCV appeared to have less impact on children experiencing more than two AOM episodes than on those with 2 or less episodes. The authors suggest that there is a subgroup of otitis-prone children that end up in a vicious cycle of subsequent episodes regardless of vaccination and

prevention of vaccine-type AOM. Other RCTs by Eskola, *et al*. [16] and Prymula, *et al*. [17] have assessed PCV efficacy in children aged 2 years and below using the more stringent definition of recurrent AOM (rAOM; defined as 3 AOM episodes in 6 months or 4 in one year) and reported a non-statistically significant reduction of 16%, and 56%, respectively. Further research is needed to establish whether prevention of early onset AOM by PCVs is associated with a reduction in more severe disease course of OM. Ideally, such research includes outcomes such as rAOM and the number of ventilation tube insertions.

A major strength of this study is the completeness, validity and generalisability of the data. Registration at a primary care practice is mandatory for all Dutch citizens, disease episodes are uniformly and systematically recorded in electronic health care records. We included a large cohort of children registered at their primary care practice within the first six months of life to reduce the likelihood of missing early life AOM episodes. Characteristics of patients enlisted in the two large primary care registries are comparable with the overall Dutch population and demographics of the participating GPs are representative for the total population of Dutch GPs [8,9].

Our PWP-TT model allowed us to efficiently use the dataset since more than 50% of the episodes are recurrences which would not have been taken into account in an original Cox proportional hazards model. Other count data models, such as Poisson, may allow for more straightforward analysis of repeated event data, but only consider the total number of events within a fixed period of time and ignore the time between repeated episodes [12]. Furthermore, hazard ratios are relative measures of risk and therefore, one may also be interested in knowing the absolute risk of having AOM after a given time point. The survival percentiles we reported provide this important information [11].

Limitations of this study include its observational design which may have introduced confounding bias: fluctuations in factors coinciding with the introduction of PCV may affect the incidence of

AOM, such as in daycare attendance, breastfeeding, health-seeking behavior and smoking practices. Such confounding is limited because changes in these variables are unlikely to be closely associated with the PCV implementation. The lack of effect of PCVs beyond the first AOM episode, may be explained by various factors such as waning of circulating pneumococcal antibodies, and an increase in the distribution of non-vaccine serotype and non-pneumococcal pathogens over time causing subsequent episodes. It should however also be noted that the number of children at risk for a subsequent episode was rather small, in particular in the PCV10 group. Our study may therefore be not sufficiently powered to draw robust conclusions regarding the impact of PCVs on subsequent episodes. Next, as information on the causative pathogens was not available, our study cannot determine whether the difference between PCV7 and PCV10 was driven by either the 3 additional pneumococcal serotypes, the impact on non-typeable *H. influenzae* (through carrier protein D) and/or by carry-over effects from PCV7 vaccinated children to PCV10 vaccinated children (herd protection). Furthermore, some AOM episodes between the date of birth and date of registration at the primary care practice may be missing in our dataset; with 97% of children in our database registered within the first three months of life we consider any impact on our findings negligible. Finally, with watchful waiting for mild to moderate AOM in practice in The Netherlands since the 1990s, many parents self-manage their children's AOM episodes [18]; this study does not capture the impact of PCV on AOM symptoms in the community.

CONCLUSION

In conclusion, our primary care-based cohort study suggests that PCV given in infancy postpones the onset and reduces the risk and of first AOM without affecting recurrences. The impact of PCV on overall AOM in children up to the age of four years seems therefore largely attributable to the prevention of a first AOM episode.

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Conflict of Interest: Alexandre Fortanier is an employee of Seqirus Netherlands B.V., Amsterdam, The Netherlands. Seqirus was not involved in any aspect of the submitted work. Arno Hoes is chair of a large (around 600 employees) research and teaching institute within our University Medical Center. The Institute performs both investigator- and industry-driven research projects with a number of pharmaceutical and diagnostic companies. In addition, some of the members of staff receive unrestricted grants for research projects from a number of companies. It is the institute's explicit policy to work with several companies and not to focus on one or two industrial partners. Arno Hoes receives no personal payment from any industrial partner. Anne Schilder and the evidENT team at University College London are supported by the National Institute of Health Research through the UCLH BRC, programme, and fellowship awards. The team work with a range of industrial partners to develop and test new therapies for ear disease. Anne Schilder receives no personal payment from any industrial partner. Roderick Venekamp has indicated he has no potential conflicts of interest to disclose.

Author contribution: Alexandre Fortanier and Roderick Venekamp designed the study, contributed to data acquisition, interpreted and analysed the data. Alexandre Fortanier drafted the first

version of the manuscript. Roderick Venekamp reviewed and revised the manuscript. Anne Schilder and Arno Hoes contributed to data interpretation, reviewed and revised the manuscript. All authors approved the final version of the manuscript.

REFERENCES

[1] Teele DW, Klein JO, Rosner B. Epidemiology of otitis media during the first seven years of life in children in greater Boston: a prospective, cohort study. J Infect Dis 1989; 160: 83–94.

[2] Kvaerner KJ, Nafstad P, Hagen JA,Mair IW, Jaakkola JJ. Recurrent acute otitis media: the significance of age at onset.Acta Otolaryngol 1997;1 17: 578-84.

[3] Marchant CD, Shurin PA, Turczyk VA, Wasikowski DE, Tutihasi MA, Kinney SE. Course and outcome of otitis media in early infancy: a prospective study. J Pediatr 1984; 104: 826-31.

[4] de Hoog M, Fortanier A, Smit H, Uiterwaal C, van der Ent C, Schilder A, et al. Impact of Early-Onset Acute Otitis Media on Multiple Recurrences and Associated Health Care Use. J Pediatr. 2016; 177: 286-91. DOI: 10.1016/j.jpeds.2016.06.066.

[5] Dagan R, Pelton S, Bakaletz L, Cohen R. Prevention of early episodes of otitis media by pneumococcal vaccines might reduce progression to complex disease. Lancet Infect Dis. 2016; 16: 480-92. DOI: 10.1016/S1473-3099(15)00549-6.

[6] Fortanier A, Venekamp R, Boonacker C, Hak E, Schilder A, Sanders E, et al. Pneumococcal conjugate vaccines for preventing otitis media. Cochrane Database Syst Rev. 2014, Issue 4. Art. No.: CD001480. DOI: 10.1002/14651858.CD001480.pub4.

[7] Hall-Stoodley L, Hu FZ, Gieseke A, et al. Direct Detection of Bacterial Biofilms on the Middle-Ear Mucosa of Children With Chronic Otitis Media. JAMA. 2006; 296: 202–11. DOI:10.1001/jama.296.2.202.

[8] Smeets H, Kortekaas M, Rutten F, Bots M, van der Kraan W, Daggelders G, et al. Routine primary care data for scientific research, quality of care programs and educational purposes: the Julius General Practitioners' Network (JGPN). BMC Health Serv Res. 2018; 18: 735. DOI: 10.1186/s12913-018-3528-5.

[9] Akkerman A, Verheij T, Veen R, Grobbee R, Hak E. Interactive medical information from the Huisartsen Network Utrecht and the Almere Zorggroep. Validity and generalisability of information on GP-infonet [in Dutch]. Huisart wet. 2008; 51:90-5.

[10] van Lier E, Geraedts J, Oomen P, Giesbers H, van Vliet J, Drijfhout I, et al. Immunisation coverage and annual report National Immunisation Programme in the Netherlands 2016 [in Dutch]. RIVM rapport 2017-0010. 2017. DOI: 10.21945/RIVM-2017-0010.

[11] Orsini N, Wolk A, Bottai M. Evaluating percentiles of survival. Epidemiol. 2012; 23: 770-1. DOI: 10.1097/EDE.0b013e3182625eff.

[12] Amorim L, Cai J. Modelling recurrent events: a tutorial for analysis in epidemiology. Int J Epidemiol. 2015; 44: 324–33. DOI: 10.1093/ije/dye.

[13] Kelly P, Lim L. Survival analysis for recurrent event data: an application to childhood infectious diseases. Stat Med. 2000; 19:13–33.

[14] Sigurdsson S, Eythorsson E, Hrafnkelsson B, Eriendsdottir H, Kristinsson K, Haraldsson A. Reduction in all-cause acute otitis media in children less than three years of age in primary care following pneumococcal vaccination with PHiD-CV10: A whole population study. Clin Infect Dis. 2018 Mar 30 [Epub ahead of print]. DOI: 10.1093/cid/ciy233.

[15] Jokinen J, Palmu A, Kilpi T. Acute otitis media replacement and recurrence in the Finnish otitis media vaccine trial. Clin Infect Dis. 2012; 55: 1673-6. DOI: 10.1093/cid/cis799.

[16] Eskola J, Kilpi T, Palmu A, Jokinen J, Haapakoski J, Herva E, et al. Finnish Otitis Media Study Group. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. N Engl J Med. 2001; 344: 403-9. DOI: 10.1056/NEJM200102083440602

[17] Prymula R, Peeters P, Chrobok V, Kriz, P, Kaliskova E, et al.Pneumococcal capsular polysaccharides conjugated to protein D for prevention of acute otitis media caused by both Streptococcus pneumoniae and non-typable Haemophilus influenzae: a randomised double-blind efficacy study. Lancet 2006; 367: 740-8. DOI: 10.1016/S0140-6736(06)68304-9

[18] Fortanier A, Venekamp R, de Hoog M, Uiterwaal C, van der Gugten A, van der Ent C, et al. Parent-Reported Symptoms of Acute Otitis Media during the First Year of Life: What Is beneath the Surface? PLoS ONE. 2015; 10: e0121572. DOI: 10.1371/journal.pone.0121572.

TABLES

Table 1. Survival time (in months) by which the first 10%, 20% or 30% of the children had experienced a first AOM episode.

Survival percentiles in months (95% CI)			
Period	**10th percentile**	**20th percentile**	**30th percentile**
no-PCV	7 (7 to 8)	10 (10 to 11)	15 (14 to 17)
PCV7	8 (7 to 8)	11 (11 to 12)	17 (16 to 17)
PCV10	8 (8 to 9)	13 (12 to 13)	20 (19 to 22)

Table 2. Event specific hazards for the first AOM episode and subsequent AOM episodes.

Hazard ratio for *k*-th AOM episode (95% CI)*						
Period	**First**	**Second**	**Third**	**Fourth**	**Fifth**	**Any**
PCV7 versus no-PCV	0.94 (0.84 to 1.05)	1.25 (0.96 to 1.63)	0.90 (0.70 to 1.18)	0.90 (0.63 to 1.27)	1.40 (0.87 to 2.24)	1.00 (0.95 to 1.06)
PCV10 versus no-PCV	0.79 (0.70 to 0.89)	1.72 (1.28 to 2.32)	0.95 (0.70 to 1.28)	0.76 (0.50 to 1.16)	1.48 (0.81 to 2.70)	0.89 (0.84 to 0.95)

* To calculate a HR for any AOM episodes, all 14,689 AOM episodes were used. With 95% of children having fewer than five AOM episodes, episodes beyond the fifth (*n*=688) were not used for the analyses of AOM recurrences as this could make the model unstable.

FIGURES

Figure 1. Histograms illustrating the frequency and distribution of AOM episodes in our study population, relative to total study population (Figure 1a) and relative to children that have had only one episode during the follow-up period (Figure 1b)

Figure 2. Kaplan-Meier curves showing the cumulative events of first AOM episodes and number of children at risk up to the age of four years.