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Original article

Effects of 13-valent pneumococcal conjugate vaccination of adults on lower respiratory tract infections and antibiotic use in primary care: secondary analysis of a double-blind randomized placebo-controlled study

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ABSTRACT

Objectives: The efficacy of 13-valent pneumococcal conjugate vaccine (PCV13) in adults to prevent community-acquired pneumonia (CAP) and lower respiratory tract infections (LRTI) not requiring hospitalization is unknown. We determined the effect of PCV13 on CAP, LRTI and antibiotic use in the primary care setting.

Methods: Community-dwelling immunocompetent adults over 65 years of age were randomized to PCV13 or placebo as part of the double-blind Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA). CAP and LRTI episodes and antibiotic prescription data were extracted from general practitioner information systems of 40 426 individuals. Vaccine efficacy (VE) of PCV13 was determined using Poisson regression with robust standard errors, comparing CAP and non-CAP LRTI episodes, LRTI-specific and total antibiotic prescriptions.

Results: In all, 20 195 participants received PCV13 and 20 231 received placebo. A total of 1564 and 1659 CAP episodes occurred in the PCV13 and placebo group, respectively; VE 5.5% (95% CI −2.6% to 13.0%). Non-CAP LRTI episodes occurred 7535 and 7817 times in the PCV13 and placebo groups, respectively; VE 3.4% (95% CI −2.0% to 8.5%). A total of 8835 and 9245 LRTI-related antibiotic courses were prescribed in the PCV13 and placebo arms, respectively; VE 4.2% (95% CI −1.0% to 9.1%). Antibiotic courses for any indication were prescribed 43 386 and 43 309 times, respectively; VE −0.4% (−4.9% to 3.9%).

Conclusions: PCV13 vaccination in the elderly is unlikely to cause a relevant reduction in the incidence of CAP, LRTI, LRTI-related antibiotic use or total antibiotic use in primary care. **Cornelis H. van Werkhoven, Clin Microbiol Infect 2021;27:995**

Introduction

Lower respiratory tract infections (LRTI) occur in 90–200 per 1000 person-years in the elderly, depending on age and gender, and over 75% of episodes are treated in primary care [1]. Community-acquired pneumonia (CAP) is particularly associated with morbidity and mortality in the elderly, with *Streptococcus pneumoniae* being the most frequent bacterial pathogen [2].

Pneumococcal conjugate vaccines (PCVs) have been available since 2000 and their introduction in infant immunization programmes has reduced the incidence of invasive pneumococcal disease in non-immunized populations by 15%–50%, with presumably similar relative incidence reductions of non-bacteraemic pneumococcal pneumonia [3–5]. In the Netherlands, infants received heptavalent PCV from 2006 to 2011 and 10-valent PCV from 2011 onwards with PCV uptake of 94%–95% throughout the study [6]. In the elderly, efficacy of the 13-valent PCV (PCV13) has

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been demonstrated for vaccine-type pneumococcal CAP and invasive pneumococcal disease requiring hospitalization [7]. It has been postulated that PCV13 also reduces the incidence of these episodes and associated antibiotic use in primary care.

Vaccination is increasingly mentioned as a possible response to the global emergence in antibiotic resistance, although studies to support this are lacking [8]. Lower incidences of infections in primary care might lead to less antibiotic use in the setting where 90% of all antibiotics for humans are prescribed [9]. The aim of this study was to evaluate the efficacy of PCV13 to prevent CAP and LRTI, LRTI-related antibiotic use, and total antibiotic use in primary care.

Methods

Study design, population and setting

The Community Acquired Pneumonia immunization Trial in Adults (CAPiTA, ClinicalTrials.gov number NCT00744263) was a double-blind randomized controlled trial in which 84 496 community dwelling subjects of 65 years and older were enrolled and randomly allocated to receive either PCV13 or placebo vaccination in a 1:1 ratio [7]. In short, among immunocompetent community-dwelling Dutch adults over 65 years of age the efficacy of PCV13 in preventing first episodes of vaccine-type pneumococcal CAP was evaluated; these episodes were captured in 58 secondary and tertiary care centres in the regions in which participants were enrolled and included episodes diagnosed in the hospital but treated in the ambulatory setting. Participants were enrolled and received PCV13 or placebo between September 2008 and January 2010, and the follow up ended on 28 August 2013. The EtioCAP study was performed parallel to this trial and comprised primary and secondary care data collection. Secondary care data were published elsewhere [10]. The primary care data reported here were collected from General Practice databases to evaluate the effect of PCV13 on the incidence of CAP, LRTI and antibiotic prescriptions in primary care. The study was approved by the Medical Ethics Committee of the University Medical Centre Utrecht, the Netherlands. The informed consent obtained at the time of enrolment into the trial included a broad consent for use of clinical data related to research on pneumococcal infections.

Data collection

In the Netherlands, every patient is registered with a single general practitioner (GP) or primary health care centre, all of which have well-established digital medical records systems. Diagnoses are registered in primary care centres according to the International Classification of Primary Care (ICPC) [11]. For feasibility reasons we selected GP practices that used any one of the four most used digital GP Information Systems: Medicom, Promedico, Microhis and Mira. Data on LRTI episodes and antibiotic prescriptions from study enrolment up to the end of follow up, and co-morbidities based on ICPC registration date before enrolment, were retrieved between October 2013 and June 2014, i.e. after patient follow up ended but before unblinding. We could not retrieve data if the participant's GP records were locked, which occurred for example if a subject changed to a non-participating GP during or shortly after the study. All data were uploaded into a secured database with the CAPiTA study number as identifier. Allocation of study vaccination, follow-up data and deaths were collected as part of the CAPiTA study.

Outcomes

The primary outcome for this analysis was CAP diagnosed and treated in primary care. Prespecified secondary end points were non-CAP LRTI treated in primary care, LRTI-related antibiotic use, and any antibiotic use. At the request of the editor we additionally analysed clinically suspected CAP and LRTI in primary and secondary care combined. Definitions are shown in the Supplementary material (Appendix S1).

Sample size calculation

The following assumptions were made for the sample size calculation. (a) Annual incidences of CAP (ICPC code R81) in primary care are 18 and 26 per 1000 among 65–74 and > 74 year olds, respectively, and annual incidences of LRTI (including CAP) are 60 and 86 per 1000 among 65–74 and > 74 year olds, respectively [12]. (b) Forty per cent of CAP cases are caused by *Streptococcus pneumoniae* [13]. (c) Coverage by PCV13 is 70% of *S. pneumoniae* serotypes causing infections [14]. (d) Moderate vaccine efficacy (VE) against vaccine-type CAP in primary care is 40%. Together this yields a VE against all-cause CAP of 11%. With 80 000 person-years of follow up per study arm, using $\alpha = 0.05$, we had 90% power to demonstrate a VE against CAP of 11%. For LRTI, this sample size yielded 90% power for a VE of 6%.

Analyses

We applied Poisson regression to analyse the effect of PCV13 on CAP, LRTI and antibiotic prescriptions. Total episodes rather than first episodes were used because we expected that a significant number of participants would have more than one episode. The log-transformed individual patient observation time was used as an offset in the model. We applied robust standard errors to correct for overdispersion. VE and 95% CI were calculated as (1 − relative risk) * 100%, with relative risks derived from the Poisson models. We exploratively analysed subgroup effects for age groups (65–74 and 75+ years) and two major co-morbidity groups (chronic obstructive pulmonary disease (COPD) or asthma, diabetes mellitus). Presence of effect modification was tested by using an interaction term of vaccination and the stratifying variable. For the analysis of clinically suspected CAP and LRTI in primary and secondary care combined we used bootstrapping (see Supplementary material, Appendix S1). The data analysis was performed in R version 3.5.1 with the sandwich package version 2.5-1 to derive robust standard errors [15,16].

Role of the funding source

Pfizer had no role in the study design, data collection, analysis and interpretation of the data, the writing of the manuscript or the decision to submit the paper for publication.

Results

Data were obtained from 40 426 participants in 730 GP practices across all study regions. Follow-up duration and completeness are described in Fig. 1. Baseline characteristics were similar to the whole trial population (Table 1) [7].

A total of 3223 CAP episodes occurred in 2673 individuals and 15 352 non-CAP LRTI episodes occurred in 8299 subjects (Table 2). The incidences of CAP and non-CAP LRTI episodes were lower in the PCV13 group compared with the placebo group without reaching statistical significance (Table 3). There was no evidence of interaction by age or co-morbidities (see Supplementary material, Tables S1, S2). An analysis restricted to first episodes yielded similar results (data available upon request).

Participants received a total of 86 695 antibiotic prescriptions during the study period, of which 18 080 (21%) were related to LRTI episodes. For LRTI, the most prescribed antibiotics were

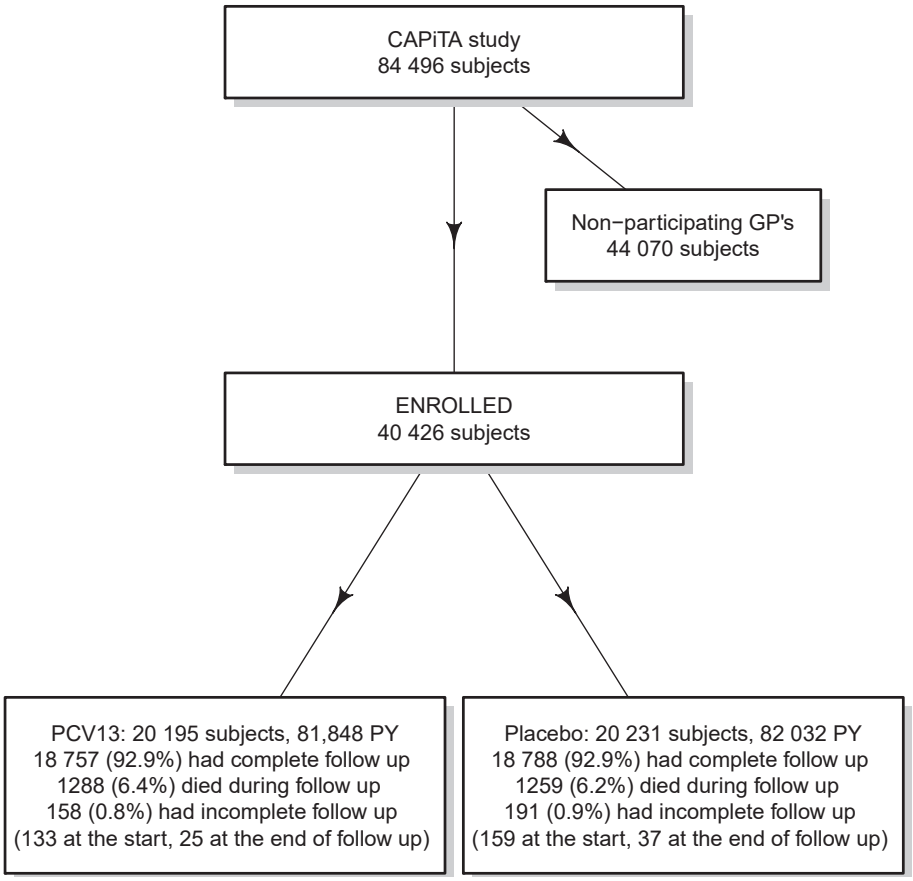

Fig. 1. Study flowchart. In the PCV13 group, eight individuals had incomplete follow up at the start of the study and died at the end of follow up, so they are counted twice in this figure. In the placebo group, this was the case for seven individuals. Abbreviations: GP, general practitioner; PCV13, 13-valent pneumococcal conjugate vaccine; PY, person-years.

doxycycline antibiotics (49%), followed by penicillins (18%) and β-lactam/β-lactamase inhibitor combinations (17%; see Supplementary material, Table S3). There was a trend towards fewer LRTI-related antibiotic prescriptions in PCV13 recipients, albeit not statistically significant, and there was no difference in total antibiotic prescriptions between study groups (Table 3). Both of these effects were consistent among subgroups (see Supplementary material, Tables S4, S5).

Discussion

In this randomized controlled trial of PCV13 in Dutch adults >65 years of age, PCV13 had a non-significant 5.5% and 3.4% VE in preventing CAP and non-CAP LRTI in primary care, respectively. Furthermore, PCV13 was associated with a non-significant 4.2% decline in antibiotic courses prescribed for LRTI. The confidence intervals of these estimates included the effect sizes of 11% for CAP and 6% for LRTI on which the sample size was based. Therefore, a clinically relevant effect seems unlikely but cannot be fully excluded. For comparison, the VE of PCV13 for all-cause CAP from the main trial was 5.1% (95% CI −5.1 to 14.2) [7], in line with what we found in the current study. However, confidence intervals for all end points crossed zero, so absence of an effect should also be considered plausible. Hence, our study provides at best weak supportive evidence of a modest reduction of CAP, LRTI and LRTI-related antibiotic consumption in primary care. The effect estimates are in line with what can be expected from vaccination against 13 pneumococcal serotypes given the current knowledge of vaccine serotype prevalence and vaccine efficacy against episodes identified in secondary care. In primary care, a recent European study identified *S. pneumoniae* in only 9.2% of CAP and 5.4% of LRTI episodes, which was substantially lower than our assumed prevalence [17].

The number of all-cause antibiotic prescriptions in primary care did not differ between PCV13 and placebo recipients. As LRTI-related antibiotic prescriptions comprised only 21% of total antibiotic prescriptions, any effect, if present, would be largely diluted for the end point total antibiotic use. The maximum plausible reductions of antibiotic prescriptions, given by the upper limit of the 95% CI, were 9.1% for LRTI-related antibiotics and 3.9% for total antibiotic prescriptions. Hence, in the Netherlands pneumococcal vaccination is unlikely to contribute to a relevant reduction in overall antibiotic use. The most prescribed antibiotics for LRTI were doxycycline (48%) and penicillins (18%), in line with recommendations from the Dutch General Practice Guideline Acute Cough, in which doxycycline was recommended as first choice until 2011, and amoxicillin thereafter [18]. The remaining 34% were hence not guideline-adherent, with amoxicillin/clavulanic acid, fluoroquinolones and cephalosporins being most prescribed. This leaves room for optimization of antibiotic treatment and reduction in antibiotic selective pressure, which may well be larger than what can be maximally achieved with pneumococcal vaccination, based on the current study.

Population benefits from PCV13 through prevention of pneumococcal pneumonia and invasive pneumococcal disease in the elderly have clearly been demonstrated [19]. Although the reductions of CAP and LRTI, if at all present, are likely to be small, the high incidence of these infections in primary care results in a much

Table 1
Baseline characteristics

	Placebo	PCV13
n	20 231	20 195
Age, median (IQR)	71.4 (68.1–76.1)	71.4 (68.1–76.1)
Male gender, *n* (%)	11399 (56.3)	11256 (55.7)
Asthma, *n* (%)	1011 (5.0)	934 (4.6)
COPD, *n* (%)	1465 (7.2)	1530 (7.6)
Diabetes, *n* (%)	2990 (14.8)	2951 (14.6)
Smoking, *n* (%)	2596 (12.8)	2457 (12.2)
Follow up in years, median (IQR)	3.9 (3.8–4.7)	3.9 (3.8–4.7)

Abbreviations: COPD, chronic obstructive pulmonary disease; PCV13, 13-valent pneumococcal conjugate vaccine.
Co-morbidities are derived from the GP records. Smoking status is self-reported at time of enrolment.

Table 2
Distribution of outcome parameters

	Placebo	PCV13
Total number of subjects	20231	20195
Number of CAP episodes, *n* (%)		
0	18 854 (93.2)	18 899 (93.6)
1	1187 (5.9)	1096 (5.4)
2	143 (0.7)	152 (0.8)
>2	47 (0.2)	48 (0.2)
Number of non-CAP LRTI episodes, *n* (%)		
0	16 004 (79.1)	16 123 (79.8)
1	2627 (13.0)	2507 (12.4)
2	830 (4.1)	782 (3.9)
>2	770 (3.8)	783 (3.9)
Number of LRTI-related antibiotic prescriptions, *n* (%)		
0	15 548 (76.9)	15 657 (77.5)
1	2752 (13.6)	2640 (13.1)
2	979 (4.8)	967 (4.8)
>2	952 (4.7)	931 (4.6)
Total number of antibiotic prescriptions		
0	9728 (48.1)	9818 (48.6)
1	3312 (16.4)	3227 (16.0)
2	2175 (10.8)	2163 (10.7)
>2	5016 (24.8)	4987 (24.7)

Abbreviations: CAP, community-acquired pneumonia; IQR: inter-quartile range; LRTI, lower respiratory tract infections; PCV13, 13-valent pneumococcal conjugate vaccine.
Data are provided as *n* (%) where *n* represents the number of subjects having had the number of episodes given in column 1.

larger number of prevented cases compared with the number of prevented hospitalized CAP cases. However, costs and disease burden of CAP and LRTI treated in primary care is relatively low, as demonstrated in a previous cost-effectiveness analysis [19]. In that study we assumed that PCV13 would reduce the number of CAP episodes in primary care by 5%. In a sensitivity analysis in which we assumed a VE of 0% for CAP episodes in primary care, the incremental cost-effectiveness ratio changed from €8647 to €8890 per quality-adjusted life-year. This 3% change of the incremental cost-effectiveness ratio was due to a 1% loss of quality-adjusted life-years and a 2% increase in health-care costs. Hence, prevention of CAP and LRTI episodes in primary care, although much more frequent than other preventable pneumococcal disease, does not drive the societal value of pneumococcal vaccination in elderly.

We exploratively tested the heterogeneity of vaccine efficacy across several subgroups. These data should be interpreted with caution, as we did not adjust for multiple testing and confidence intervals of the subgroups were generally wide and overlapping. The data suggest a higher vaccine efficacy against CAP in adults 65–75 years old and those without COPD or asthma, in line with previous findings from the same trial related to CAP episodes requiring hospital admission [20,21]. For these secondary care episodes we previously found a substantially higher VE of PCV13 in individuals with diabetes [20]. The opposite was observed in the current study: patients with diabetes had a negative VE, although the confidence interval largely overlapped with that of the subgroup without diabetes and the interaction effect was not statistically significant. Numbers were too low to be conclusive about the subgroup effects. It should be mentioned that patients of higher age or with asthma, COPD or diabetes are at increased risk of pneumococcal infections. Hence, even if the VE is indeed lower in these subgroups, the absolute risk reduction may still be higher.

The study had several limitations. First, the diagnosis of CAP or other LRTI is made by the GP based on clinical signs and symptoms, mostly without radiographs or laboratory tests to confirm the diagnosis, so misclassification of episodes is inevitable. However, GPs and patients were not aware of the allocation to PCV13 or placebo and diagnosis and treatment of LRTI in primary care was not influenced by the CAPiTA study protocol. Misclassifications are therefore expected to be random, leading to bias towards no effect. Reporting of LRTI episodes in the GP Information Systems reflects standard care practice, maximizing generalizability of our findings for the primary care setting. Another potential limitation is the accuracy of the medical records and ICPC coding of the episodes

Table 3
Vaccine efficacy of PCV13

End point	Events placebo	Event rate placebo	Events PCV13	Event rate PCV13	VE (95% CI)	P Value
Primary care						
All CAP episodes	1659	20.2	1564	19.1	5.5% (−2.6% to 13.0%)	0.178
All non-CAP LRTI episodes	7817	95.3	7535	92.1	3.4% (−2.0% to 8.5%)	0.210
All LRTI episodes	9476	115.5	9099	111.2	3.8% (−1.1% to 8.4%)	0.124
LRTI-related antibiotic prescriptions	9245	112.7	8835	107.9	4.2% (−1.0% to 9.1%)	0.109
Total antibiotic prescriptions	43 309	528.0	43 386	530.1	−0.4% (−4.9% to 3.9%)	0.859
Primary and secondary care combined						
Clinically suspected CAP	1659[a] + 756[b]	33.7[c]	1564[a] + 699[b]	31.2[d]	7.4% (−0.0% to 14.4%)	0.051
LRTI including CAP	9476[a] + 756[b]	128.9[c]	9099[a] + 699[b]	123.2[d]	4.4% (−0.3% to 9.0%)	0.067

Abbreviations: CAP, community-acquired pneumonia, LRTI, lower respiratory tract infection; PCV13, 13-valent pneumococcal conjugate vaccine; VE, vaccine efficacy.
Event rate is number of events per 1000 person-years.
[a] Cases from primary care.
[b] Cases from secondary care observed in the same population base.
[c] In the placebo group, total follow up in secondary care was 83 077 person-years and an estimated 30% of clinically suspected CAP cases was unidentified.
[d] In the PCV13 group, total follow up in secondary care was 82 887 person-years and an estimated 33% of suspected CAP cases was unidentified. Unidentified episodes were taken into account in the event rate calculation (see Supplementary material, Appendix S1).

and co-morbidities. In all four GP Information Systems systems, ICPC coding of an episode is mandatory. In primary care, management of COPD, asthma and diabetes mellitus through specialized care programmes results in fairly accurate ICPC coding of these conditions [22]. By combining Anatomical Therapeutic Chemical and ICPC-based digital data extraction and manually reviewing the source data in the medical record, the possibility of missing or misclassifying episodes was reduced. However, due to screening limitations, co-morbidities such as COPD can be underestimated in frail elderly individuals [23]. A third possible limitation is that the inclusion and exclusion criteria of the CAPiTA trial selected for immunocompetent, community-dwelling elderly people. The study population, therefore, was relatively healthy compared with the general Dutch population. Although the prevalence of asthma (4.8% in our cohort and 5.7% in the general Dutch population) and diabetes mellitus (14.7% in our cohort and 15%–16% in the general population) were fairly similar, the prevalence of COPD in our cohort (7.4%) was lower than the reported 11%–12% prevalence of COPD in the general population (https://opendata.cbs.nl/statline/). As the VE of PCV13 in individuals with COPD seems to be lower compared with those without COPD, the lower prevalence of COPD in our study may have led to overestimation of the overall VE. A fourth limitation of our study is that we were only able to include individuals for whom data were still accessible after the study. The mortality rate (6.3%) was similar to that of the main study (7.1%) [7] so not many patient records were locked for that reason. However, loss to follow up was 5% in the main study and only 0.2% in the subset with available GP data, so close to 5% of the subjects were not included in the current analysis due to non-accessibility of the data. This may have introduced some bias, although loss-to-follow-up rates were small and very similar between the PCV13 and placebo groups.

The main strengths of the study are the randomized, placebo-controlled, double-blind study design and the sample size of over 40 000 individuals followed for 4 years on average with nearly complete data collection. Baseline characteristics and regional distribution were similar to those of the CAPiTA trial. To our knowledge there are no other prospective placebo-controlled trials evaluating the efficacy of PCV13 in elderly individuals in a primary care setting.

We conclude that PCV13 vaccination in the elderly is unlikely to cause a relevant reduction in the incidence of CAP, LRTI, LRTI-related antibiotic use or total antibiotic use in primary care.

Transparency declaration

This study was embedded in the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA), which was sponsored by Pfizer. No support was received for the current study. Pfizer was not involved in the collection, analysis and interpretation of the data underlying this study. CHvW reports grants from Pfizer through institution, speaker and consultancy fees from Pfizer, speaker fees from Merck and non-financial support from bioMérieux. SMH reports personal fees from Pfizer. TJMV reports grants from/partnership with Janssen Pharmaceuticals, Biocartis, BioMérieux and Berry Consultants. MJMB reports grants from Pfizer, Merck and Sanofi.

Authorship statement

All authors contributed to the design of the study and interpretation of the data. MBol coordinated the data collection. CHvW and MBol performed the analysis and wrote the first draft of the manuscript. All authors critically revised the manuscript and approved the submission.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2020.09.011.

References

[1] Millett ERC, Quint JK, Smeeth L, Daniel RM, Thomas SL. Incidence of community-acquired lower respiratory tract infections and pneumonia among older adults in the United Kingdom: a population-based study. PLoS One 2013;8:e75131.
[2] Postma DF, van Werkhoven CH, Huijts SM, Bolkenbaas M, Oosterheert JJ, Bonten MJM. New trends in the prevention and management of community-acquired pneumonia. Neth J Med 2012;70:337–48.
[3] Davis SM, Deloria-Knoll M, Kassa HT, O'Brien KL. Impact of pneumococcal conjugate vaccines on nasopharyngeal carriage and invasive disease among unvaccinated people: review of evidence on indirect effects. Vaccine 2013;32:133–45.
[4] Feikin DR, Kagucia EW, Loo JD, Link-Gelles R, Puhan MA, Cherian T, et al. Serotype-specific changes in invasive pneumococcal disease after pneumococcal conjugate vaccine introduction: a pooled analysis of multiple surveillance sites. PLoS Med 2013;10:e1001517.
[5] van Werkhoven CH. Herd effects of child vaccination with pneumococcal conjugate vaccine against pneumococcal non-invasive community-acquired pneumonia: what is the evidence? Hum Vaccines Immunother 2017;13:1177–81.
[6] van Lier EA, Oomen PJ, Giesbers H, van Vliet JA, Drijfhout IH, Zonnenberg-Hoff IF, et al. Rijksvaccinatieprogramma nederland. the Netherlands: Bilthoven; 2016.
[7] Bonten MJM, Huijts SM, Bolkenbaas M, Webber C, Patterson S, Gault S, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med 2015;372:1114–25.
[8] Buckley BS, Henschke N, Bergman H, Skidmore B, Klemm EJ, Villanueva G, et al. Impact of vaccination on antibiotic usage: a systematic review and meta-analysis. Clin Microbiol Infect 2019;25:1213–25.
[9] European Centre for Disease Prevention and Control. Antimicrobial consumption. In: ECDC. Annual epidemiological report 2017. Stockholm: ECDC; 2018.
[10] Huijts SM, Coenjaerts FEJ, Bolkenbaas M, van Werkhoven CH, Grobbee DE, Bonten MJM. The impact of 13-valent pneumococcal conjugate vaccination on virus-associated community-acquired pneumonia in elderly: exploratory analysis of the CAPiTA trial. Clin Microbiol Infect 2018;24:764–70.
[11] Lamberts H, Wood M. ICPC. International classification of primary care. Oxford: Oxford University Press; 1987.
[12] Van Deursen AMM, Verheij TJM, Rovers MM, Veenhoven RH, Groenwold RHH, Bonten MJM, et al. Trends in primary-care consultations, comorbidities, and antibiotic prescriptions for respiratory infections in The Netherlands before implementation of pneumococcal vaccines for infants. Epidemiol Infect 2012;140:823–34.
[13] Woodhead MA, Macfarlane JT, Mccracken JS, Rose DH, Finch RG. Prospective study of the aetiology and outcome of pneumonia in the community. Lancet 1987;329:671–4.
[14] Rodenburg GD, de Greeff SC, Jansen AG, de Melker HE, Schouls LM, Hak E, et al. Effects of pneumococcal conjugate vaccine 2 years after its introduction, The Netherlands. Emerg Infect Dis 2010;16:816–23.
[15] R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2018. Available from: https://www.R-project.org/.n.d.
[16] Zeileis A. Econometric computing with HC and HAC covariance matrix estimators. J Stat Softw 2004;11:1–17.
[17] Ieven M, Coenen S, Loens K, Lammens C, Coenjaerts F, Vanderstraeten A, et al. Aetiology of lower respiratory tract infection in adults in primary care: a prospective study in 11 European countries. Clin Microbiol Infect 2018;24:1158–63.
[18] Verheij TJ, Hopstaken RM, Prins JM, Salomé PhL, Bindels PJ, Ponsioen BP, et al. NHG standaard acuut hoesten (eerste herziening). Huisarts Wet 2011;54:68–92.
[19] Mangen M-JJ, Rozenbaum MH, Huijts SM, Van Werkhoven CH, Postma DF, Atwood M, et al. Cost-effectiveness of adult pneumococcal conjugate vaccination in The Netherlands. Eur Respir J 2015;46:1407–16.
[20] Huijts SM, van Werkhoven CH, Bolkenbaas M, Grobbee DE, Bonten MJM. Post-hoc analysis of a randomized controlled trial: diabetes mellitus modifies the efficacy of the 13-valent pneumococcal conjugate vaccine in elderly. Vaccine 2017;35:4444–9.
[21] Van Werkhoven CH, Huijts SM, Bolkenbaas M, Grobbee DE, Bonten MJM. The impact of age on the efficacy of 13-valent pneumococcal conjugate vaccine in elderly. Clin Infect Dis 2015;61:1835–8.
[22] Khan NA, Visscher S, Verheij RA. De kwaliteit van het elektronisch patiëntendossier van huisartsen gemeten. 2011. Available from: https://nivel.nl/sites/default/files/bestanden/Rapport-kwaliteit-epd-twente.pdf.
[23] Bertens LCM, Reitsma JB, van Mourik Y, Lammers J-WJ, Moons KGM, Hoes AW, et al. COPD detected with screening: impact on patient management and prognosis. Eur Respir J 2014;44:1571–8.