Association of infant pneumococcal vaccination with pneumococcal pneumonia among mothers

Hak, Eelko; Shea, Kimberly M.; Jick, Susan S.

Published in:
Vaccine

DOI:
10.1016/j.vaccine.2013.01.018

Vaccine 31 (2013) 1590–1596

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Association of infant pneumococcal vaccination with pneumococcal pneumonia among mothers: A nested case–control study using the GPRD

Eelko Hak[a,*], Kimberly M. Shea[b], Susan S. Jick[b,c]

[a] Unit of Pharmaco-epidemiology & Pharmaco-economics, Department of Pharmacy, University Groningen, The Netherlands
[b] Department of Epidemiology, Boston University School of Public Health, Boston, USA
[c] Boston Collaborative Drug Surveillance Program, Boston, Lexington, USA

ARTICLE INFO

Article history:
Received 6 September 2012
Received in revised form
11 December 2012
Accepted 12 January 2013
Available online 25 January 2013

Keywords:
Conjugate pneumococcal vaccine
Immunization
Infant
Epidemiology
Case–control
General practice

ABSTRACT

Since implementation of infant immunization with 7-valent pneumococcal conjugate vaccine (PCV7), increased rates of pneumococcal pneumonia have been reported among adults. Using a cohort of mother–infant pairs identified from the General Practice Research Database in the UK we found that from 2006 to 2010 the annual incidence rate of pneumococcal pneumonia among mothers increased from 61/100,000 to 81/100,000. We identified 43 cases of pneumococcal pneumonia in mothers and 430 control mother–infant pairs. The conditional odds ratio of pneumococcal pneumonia in mothers whose infants received a three-dose series of PCV7 compared to mothers whose infants received zero, one, or two doses was 4.0 (95% confidence interval [95%CI]: 1.0–15.8), and 11.0 (95%CI: 1.2–98.6) when compared with mothers whose infants received no vaccinations. The incidence of pneumococcal pneumonia may have increased in mothers following the introduction of PCV7, possibly because mothers whose infants received PCV7 are at increased risk for pneumococcal pneumonia. Though there is a chance of bias inherent to observational studies, the study findings support close monitoring of adult pneumococcal disease and potential role of adult vaccination needs to be explored.

1. Introduction

Seven-valent pneumococcal conjugate vaccine (PCV7) was added to the United Kingdom (UK) infant immunization schedule in September 2006 as a three-dose series to be administered at 2, 4, and 13 months and offers protection against the most common serotypes accounting for invasive pneumococcal diseases (IPD) in children [1]. Following the success in the United States (US), in the UK the risk of vaccine serotype pneumococcal carriage and IPD in infants declined as well as in adults who are unvaccinated [2–5].

The dramatic reduction in IPD caused by PCV7 serotypes in the UK has coincided with an increase in pneumococcal infections attributable to non-PCV7 serotypes [6]. This increase has earlier been noted in North America [7] and has thus far been insufficient to offset the total reduced incidence of PCV7-serotype pneumococcal disease [1]. However, in a few recent studies from Europe, it appears that the overall rates of asymptomatic nasopharyngeal carriage of non-PCV7 serotypes may be increasing among adults. In a randomized controlled trial from The Netherlands, parents experienced a two-fold increase in nasopharyngeal carriage of non-PCV7 serotypes if their infants were fully vaccinated compared with control parents whose infants were not vaccinated, and a 29% increase in overall pneumococcal carriage [8]. In a study comparing serotype-specific carriage in children and parents before and after introduction of PCV7 in the UK, Flasche et al. similarly observed a five-fold increase of non-vaccine serotype carriage among parents and a 28% increase in overall carriage [9]. Neither the UK or the Netherlands have detected a corresponding increased risk of overall IPD among adults via national surveillance networks [9,10]. In the US, however, Metlay et al. were the first to observe a statistically significant 7% annual increase in community-acquired pneumococcal bacteremia among hospitalized adult patients from 2002 to 2008, particularly in young adults, and predominantly caused by increases in non-PCV7 pneumococcal disease [11]. Another study conducted in the UK found a statistically significant doubling in overall IPD incidence from 2002 to 2009 among adults aged 15–64 years despite nearly complete uptake of PCV7 vaccine among infants [12].

We therefore carried out a study to assess the incidence rates of lobar/pneumococcal pneumonia following the introduction of PCV7 in the UK in mothers of infants who are generally at highest risk for transmission of the pneumococcal bacteria from their young child. We also assessed a mother's risk of developing pneumococcal pneumonia in relation to the PCV7 immunization status of her child.

* Corresponding author at: Pharmaco-epidemiology & Pharmaco-economics, Department of Pharmacy, University Groningen, Deusinglaan 1, 9713 AV, The Netherlands. Tel.: +31 50 363 7576.
E-mail address: e.hak@rug.nl (E. Hak).

0264-410X/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.vaccine.2013.01.018

2. Methods

2.1. Data source and setting

This study was conducted using data from the GPRD, which is administered by the Medicines and Healthcare Products Regulatory Agency and has been previously described in detail [13–15]. In brief, the GPRD contains electronic medical records for a nationally representative group of British residents currently enrolled in more than 450 general practice offices in the UK. General practitioners are trained to accurately record information about patient demographics, medical diagnoses and procedures that are part of routine care or resulting from hospitalizations, results of laboratory testing, and referrals to hospitals using READ codes, which are standard clinical codes – akin to ICD-9 codes – used in general practice in the United Kingdom. READ codes support detailed clinical encoding of multiple patient phenomena including demographic (sex, race/ethnicity, religion, occupation, other social circumstances) and clinical information (medical diagnoses, clinical signs, symptoms and observations, laboratory tests and results, diagnostic, therapeutic or surgical procedures performed). In addition, the GPRD includes detailed information about prescriptions and vaccinations. The quality and completeness of the information recorded in the GPRD has been widely validated [13–15]. The database captures nearly all episodes of pneumonia that are diagnosed and treated by general practitioners, require hospitalization, or result in death [16]. Also, infant immunizations are administered in general practices, and patient records describing receipt of immunizations have been found to be virtually complete [17–20]. This study was approved by the Independent Scientific Advisory Committee (ISAC) within the UK Medicines and Healthcare Products Regulatory Agency.

2.2. Study population and identification of lobar/pneumococcal pneumonia

The study comprised two analyses. In the first we estimated annual incidence rates of first-time lobar/pneumococcal pneumonia using the GPRD to identify a study population of all mothers aged 20 through 39 years who gave birth to their first child on or after January 1, 2005 and who were present in the GPRD at any time from 2006 through 2010. We linked mothers to their first-born child using a unique identification number given to members of the same family and the date of delivery code in the mother's record in combination with the date of birth in her child's record.

Among the study population, we identified mothers who had a record of a first-time diagnosis of community-acquired lobar/pneumococcal pneumonia between 2006 and 2010 using the specific GPRD READ code H21.00 (this code is consistent with ICD-9 code 481). Annual incidence rates of first-time lobar/pneumococcal pneumonia in mothers were estimated by dividing the number of incident cases that occurred during each year of the study period by the total amount of person-time contributed by mothers in the study population during the same study year.

2.3. PCV7 coverage among first-born infants

Annual PCV7 coverage was estimated as the proportion of first-born children who received one, two, or three doses of PCV7 by 24 months of age for each year of the study period. Estimates of annual vaccine coverage were restricted to first-born children who were present in the database during each study year.

2.4. Case–control analysis

In the case–control analysis, a subset of all eligible case mothers with a first-time diagnosis of lobar/pneumococcal pneumonia was included if these cases had at least two years of complete medical history, including complete information on smoking status, comorbidities and drug prescriptions, recorded in the database prior to their diagnosis. This was done to ensure adequate clinical information on potential risk factors that may be confounders of the association between infant PCV7 vaccination and lobar/pneumococcal pneumonia. The cut-off for two years of history is a commonly used period for primary care database research to select "active" patients. In order to confirm the diagnosis of lobar/pneumococcal pneumonia, all electronic medical records of the cases were reviewed for information on whether the diagnosis occurred in the hospital or in primary care, and for details of treatment and high-risk comorbidities. In addition, because asthma is a frequent risk factor for pneumonia, we wanted to make sure that the incident cases of pneumonia were not a complication of existing asthmatic disease. Medical record review indicated that only one case occurred as a complication of existing asthma while all other cases appeared to be new disease. The date of the first-time diagnosis was considered the index date.

Ten control mothers without a history of any pneumonia and who had at least two years of complete medical history in the database were randomly selected from the same study population as the cases and matched to each case on index date of the case diagnosis, age, birth date of first child, current smoking status and presence or absence of chronic lung disease [20], as well as use of any benzodiazepine or anti-depressant medications [21]. We chose to match controls to cases on prior use of benzodiazepines or anti-depressants because more than half the cases in our study had been prescribed at least one of these medications, and because there is some evidence that the treated conditions may confer increased risk of pneumonia or may be a marker for health care consumption [21]. Smoking status was classified as current, former, or non-smoker based on GPRD codes recorded prior to the index date.

2.5. Exposure to infant PCV7 vaccination

Mothers were classified as being exposed or unexposed based on the PVC7 immunization status of their first-born infant. Based on the recommended immunization schedule, mothers whose first-born infants received three doses of PCV7 were considered exposed, and mothers who received fewer than three doses of PCV7 were considered not exposed [1,20]. PCV7 vaccination status in infants was ascertained using the following READ codes recorded in the GPRD: 657L.00, 657M.00, 657N.00, 6572.00, 6572000 or 900.00. Only vaccinations administered at least 14 days prior to the index date of the mother were considered.

2.6. Statistical analyses

Conditional logistic regression was used to estimate odds ratios and associated 95% confidence intervals (CI) describing the association between infant PCV7 vaccination and lobar/pneumococcal pneumonia in the mother after adjustments for the matched covariates using SAS, Version 9.1 (SAS Institute, Inc., Cary, NC). Mothers whose infants received at least three doses of PCV7 were compared to (1) mothers whose infants received zero, one or two doses and to (2) mothers whose infants received zero doses. Because of concern that residual confounding may have been present for certain covariates and because we were restrained by the number of cases and controls, we a priori defined a few subgroups for restricted analyses

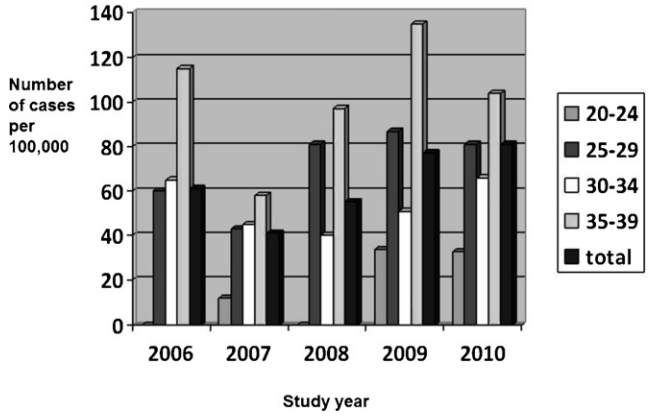


Fig. 1. Annual age-specific incidence rates of first-time lobar/pneumococcal pneumonia per 100,000 person-years among mothers aged 20 through 39 years from 2006 through 2010 (N = 187,137 total person-years).

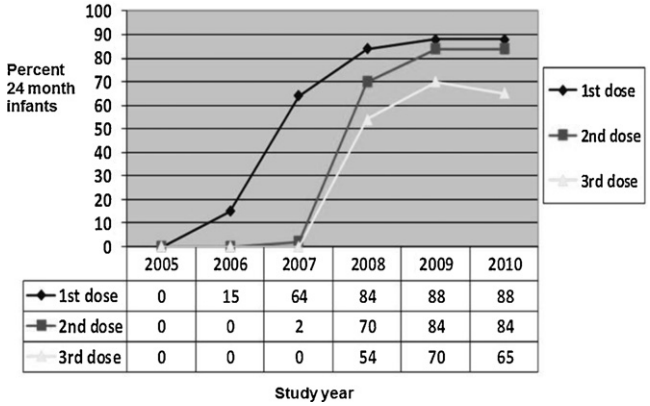
including the mother's age, number of children in the household, absence of asthma, time period, and duration of exposure interval.

3. Results

In all, 115 cases of first-time lobar/pneumococcal pneumonia were recorded among mothers aged 20 through 39 years. Mothers contributed a total of 187,137 person-years during the total study period. There were no cases of first-time lobar/pneumococcal pneumonia in 20–24 year olds in 2006 and only one in 2007. The number increased to three cases in 2009 and two in 2010. There were more cases in the older ages with incidence rates increasing from 33 per 100,000 in ages 20–24 to 104 per 100,000 in the 35–39 years age-group in 2010. The overall rates in all mothers increased from 61/100,000 in 2006 to 81/100,000 in 2010 (Fig. 1).

Among a total of 232,998 twenty-four month-old first-born infants in the linked mother–infant database, the number of infants who contributed to the analysis ranged from 43,993 to 48,468 per study year. In this population the uptake of first PCV7 vaccine ranged from 7150 infants in 2006 (15%) to 38,414 infants (88%) in 2010 (Fig. 2). Corresponding figures for a second and third vaccine uptake were 325 (<1%) and 92 (<1%) in 2006, and 36,824 (84%) and 28,752 (65%) in 2010, respectively.

A total of 43 mothers with a diagnosis of incident lobar/pneumococcal pneumonia met the criteria for the case–control analysis. Among these, 12 (28%) cases had uncomplicated pneumonia and were treated with antibiotics in primary care and 29 (63%) cases had pneumonia requiring hospitalization.



	2005	2006	2007	2008	2009	2010
1st dose	0	15	64	84	88	88
2nd dose	0	0	2	70	84	84
3rd dose	0	0	0	54	70	65

Fig. 2. Uptake (%) of one, two or three doses of PCV7 among infants at 24 months of age according to calendar year from 2006 to 2010.

Table 1
Characteristics of mothers with lobar/pneumococcal pneumonia (cases) and matched controls on the index date.

Characteristic	N (%)	
	Cases (n = 43)	Controls (n = 430)
Mean age of mother in years (SD)	31 (5)	31 (5)
Child's age at index date		
36 months or less	29 (67)	294 (68)
More than 36 months	14 (33)	136 (32)
Smoking status:[a]		
Current smoker	13 (30)	130 (30)
Non-smoker	17 (40)	170 (40)
Former smoker	13 (30)	130 (30)
Current chronic pulmonary disease	11 (26)	110 (26)
Any antidepressants or benzodiazepines prescribed	26 (60)	260 (60)
Presence of other infants in the household[b]	23 (53)	245 (56)

[a] Smoking status was known for all cases and used to match controls.
[b] We did not match on this factor.

In two cases recorded with lobar/pneumococcal pneumonia who were treated in primary care, their type of treatment was unclear from their medical records. The mean age of cases was 31 years (±5 years), 30% were current smokers, 26% had chronic pulmonary disease, and 60% had ever received a benzodiazepine or anti-depressant prescription prior to the index date (Table 1). The 43 case mothers were matched to 430 control mothers with no diagnosis of pneumonia. Demographic and clinical characteristics of cases and controls are provided in Table 1.

The conditional odds ratio of lobar/pneumococcal pneumonia in mothers whose first infant received three doses of PCV7 compared to mothers whose infants received zero, one, or two doses of PCV7 was 4.0 (95%CI: 1.0–15.8). The odds ratio increased to 11.0 (95%CI: 1.2–98.6) when mothers whose infants received three doses of PCV7 were compared with mothers whose infants did not receive any PCV7 vaccinations. The odds ratios for mothers whose first-born infant received three doses of PCV7 compared to mothers whose infants received zero, one, or two doses of PCV7 vaccinations for the development of lobar/pneumococcal pneumonia ranged from 3.3 to 8.2 in analyses restricted to young women, those with no asthma, short exposure interval, and those in later study years (Table 2).

4. Discussion

This study showed that the incidence of first-time lobar/pneumococcal pneumonia in mothers has increased since the introduction of PCV7 infant immunization in the UK. We also observed that among infants, one in three age-eligible infants had not completed the recommended three-dose series by the age of 24 months in 2010. Finally, results from our case–control analysis indicated that there was an association between the risk of lobar/pneumococcal pneumonia in mothers and the PCV7 immunization status of her first-born infant. This association was highest when comparing the odds of disease among mothers whose infants received three doses of PCV7 to mothers whose infants did not receive any doses, and were not meaningfully attenuated when we restricted the analysis to relevant subgroups.

Although we did not have serotype-specific data, these results are consistent with the notion that the net indirect benefits of the PCV7 immunization program due to decreased circulation of PCV7-serotype pneumococci in adults are likely offset by the coinciding clonal expansion of non-PCV7 serotypes [6–9,11,23]. These non-PCV7 serotypes may be more prevalent in adults or more invasive, thereby increasing the likelihood of disease. For example, Flasche et al. observed a high case-to-carrier ratio, a measure of

Table 2
Conditional odds ratios for the association between PCV7[a] vaccination status of first-born infants and lobar/pneumococcal pneumonia among mothers overall, and across strata.

Stratum	*N* (%)		OR[b] (95%CI)
	Cases (*n* = 43)	Controls (*n* = 430)	
Full population			
<3 doses of PCV7	21 (49%)	252 (59)	Reference
3 doses of PCV7	22 (51%)	178 (41)	4.0 (1.0–15.8)[†]
Mothers <30 years			
<3 doses of PCV7	10 (59)	113 (71)	Reference
3 doses of PCV7	7 (41)	46 (29)	7.2 (0.5–96.3)
Mothers without asthma			
<3 doses of PCV7	17 (53)	200 (63)	Reference
3 doses of PCV7	15 (47)	120 (37)	3.3 (0.7–13.9)
Mothers with exposure time of less than 36 months since birth of first infant			
<3 doses of PCV7	12 (41)	165 (56)	Reference
3 doses of PCV7	17 (59)	129 (44)	8.5 (1.1–70.3)[‡]
Mothers with index dates in 2009 and 2010			
<3 doses of PCV7	9 (33)	117 (43)	Reference
3 doses of PCV7	18 (67)	153 (57)	3.6 (0.7–20.2)

[a] 7-Valent pneumococcal conjugate vaccine.
[b] Controls were matched to cases on index date, date of birth, age, presence of chronic pulmonary disease, prescription of antidepressants or benzodiazepines, and smoking status.
[†] *p*-value 0.05.
[‡] *p*-value 0.02; all other *p*-values >0.05.

pneumococcal invasiveness, for the most prevalent non-PCV7 serotypes 19A, 7F and 22F several years after PCV7 implementation in the UK, and found that serotypes 7F and 22F were also highly prevalent in adults [9]. Non-PCV7 serotypes 8 and 12F that were not otherwise found in carriers also commonly occurred among adult IPD cases. Whether the net effect of this shift is a decrease or increase of pneumococcal disease depends on acquired immunity against PCV7-serotype and non-PCV7 serotypes. For infants, young children and the elderly, the net effect is positive, despite replacement disease by e.g. 19A. For adults this may be different because of already low incidence of pneumococcal disease. In a study from the Netherlands among adults with IPD, intermediate to high fatality rates were observed among adults with IPD due to serotypes 19A (19% fatality rate), 7F (10%), 12F (12%), 8 (15%) and 22F (18%); and together, these serotypes were present in more than a quarter of adult IPD patients [24]. Except for 7F and 19A, these non-PCV7 serotypes are not covered by the current successors of PCV7, i.e. PCV10 and PCV13, and the future epidemiology of these pneumococcal serotypes among adults remains uncertain.

The observed increased incidence rates of lobar/pneumococcal pneumonia among mothers are consistent with another US study [10]. In the Netherlands, a comparable annual increase in the rate of IPD was noted among persons aged 5–49 two years post-PCV7 vaccination, though this increase was not statistically significant [10]. Elston and colleagues also detected increases in pneumonia hospitalizations among 18–64 year-old British adults in whom incidence increased from 70 per 100,000 population in 2006 to 84 per 100,000 in 2009 (data provided on request by Dr. J. W.T. Elston).

During the study period, we observed that the rate of uptake of a first dose of PCV7 vaccine among 24 month-old first-born infants was slightly lower than that reported by the National Health Service (NHS) (91% versus 88% in our study in 2009–2010), and that the NHS reported a substantially higher rate of the booster dose of PCV7 than was found in our study (88% versus 68% in our study in 2009–2010) [25]. However, the NHS defines a booster dose of PCV7 as receipt of one dose on or after 12 months of age, irrespective of the number of doses before that age, and before a child's second birthday. After reviewing 50 infant medical records randomly selected from the control mother–infant pairs, we found that approximately one third of control infants received a booster dose after 12 months, but had only received one PCV7 vaccination before 12 months of age. According to the current immunization recommendations, but in contrast to the definition used by the NHS, these infants were not classified as being fully vaccinated in our study.

Despite several strengths of our study including identification of a large cohort of unique mother–infant pairs and use of highly accurate clinical information, our study has potential limitations inherent to the conduct of observational studies. First, exclusive use of READ codes used in the GPRD to ascertain cases of lobar/pneumococcal pneumonia created potential for misclassification of the outcome diagnosis [21,22]. Twenty-nine cases of lobar/pneumococcal pneumonia required hospitalization, and standard diagnostic tests were used to confirm the presence of the pneumococcal bacteria. The remaining 14 cases were treated in primary care and did not have records confirming the presence of pneumococcal bacteria. We suspect that pneumococcal etiology for these cases was most likely confirmed by rapid urinary tests or by examination of X-rays, though this information is lacking in the medical records. We recently demonstrated in a meta-analysis that in the United Kingdom based on 5 cohort studies that more than 30% of all community-acquired pneumonia cases were caused by *Streptococcus pneumonia* (Rozenbaum et al., *European Journal of Clinical Microbiology & Infectious Diseases*, accepted for publication). It is therefore likely that the majority of lobar (pneumococcal) cases were caused by *S. pneumonia*. Restriction of the analysis to confirmed hospitalized cases and controls showed similar associations (OR 3.2, 95% confidence interval 0.75–13.7) with largely overlapping confidence intervals when comparing mothers of children who received three versus 2, 1, or 0 PCV7 doses. In addition, we cannot exclude the possibility that some cases had a prior episode of pneumococcal pneumonia before our study started in 2006. However, it is unlikely that this would have strongly affected our results given the relatively low risk for pneumococcal pneumonia in this population.

Second, we may have underestimated the prevalence of infant PCV7 vaccination, for example, if infants received a vaccine dose from a physician other than their own GP who may not have recorded their vaccine in the GPRD database. Importantly, since GPs are paid a small fee for each immunization that they administer, child immunization records in the UK are expected to be highly accurate [20]. Because vaccinations are given in primary care which is accessible to everyone, under-ascertainment of PCV7 immunizations would likely be random, and therefore expected to result in a bias toward the null.

Third, a booster dose might not be necessary to obtain immunity and classifying children with one or two received PCV7-doses in the reference group may have led to underestimations. We therefore decided to add a subgroup analysis including only mothers whose children received none of the vaccination versus those who received 3 doses and risks increased (OR 4.6, 95% 0.82–25.6, 29 cases and 269 controls).

Fourth, the presence of other children in the household may have confounded our results. We determined the number of cases and controls who had more than one child in the household during the study period, and found that cases and controls did not differ in these proportions.

Fifth, our results may be susceptible to residual confounding by health behaviors that may differ between cases and controls. We opted to use matching to control for receipt of prescriptions for antidepressants or benzodiazepines as a proxy for health behaviors because depression and sleeping problems appeared common among cases, and because such psychological diseases have been associated with increased risk for pneumonia and high health care consumption [22]. While this may have reduced some of the difference between cases and controls, other factors like hand hygiene or practicing other preventive or risk taking behaviors could not

be controlled for in our analysis. However, it seems reasonable to assume that preventive behaviors would be more common among mothers whose infants received all recommended vaccinations, which would have again resulted in a bias toward the null. In addition, due to the magnitude of our observed associations, we do not believe that our results are fully attributable to residual confounding, especially not because other risk elevating conditions than lung disease and depression were not present in the medical records.

Finally, the observed increased trend in pneumococcal pneumonia might be due to diagnostic bias. However, a recent publication using data from the GPRD demonstrated that the incidence of pneumoconiosis, which has similar diagnosing patterns as pneumococcal disease, decreased from 2005 to 2008, suggesting that diagnostic bias is unlikely [26].

Despite these limitations, this study suggests that lobar/pneumococcal pneumonia is increasing among young mothers in close contact with infants, and that infant PCV7 immunization may be associated with a higher risk of pneumococcal pneumonia in mothers. Because our findings indicate potential increases in risk of pneumonia after PCV7 vaccination, studies are now warranted to monitor the impact of large-scale pneumococcal vaccination, including the impact of increased valency pneumococcal vaccines, on adults worldwide.

Funding

The current study was funded by the University of Groningen through an unrestricted grant to the first author.

Conflict of interest

All authors declare to have no conflict of interest specific to the subject. Eelko Hak is a member of the Dutch Health Council advising on the Netherlands immunization program. He was involved in the development of the CAPITA trial study design when affiliated with the University Medical Center Utrecht, The Netherlands until February 2009 (Hak E, et al. *Neth Med J*, 2007), but has not been involved in the study conduct since its start later in 2009. The Boston Collaborative Drug Surveillance Program, Boston University School of Public Health has received no funding in relation to this study.

Acknowledgements

We are indebted to Dean McLauglin, senior data manager, at the Boston Collaborative Drug Surveillance Program who developed the programming for data retrieval from the GPRD database. Also we wish to thank Dr. Lin Li, epidemiologist, for her kind assistance with the statistical analyses.

Appendix. Codes

Smoking status (code closest to index date):
YES
137P.00 cigarette smoking
1372.00 trivial smoker
137R.00 current smoker
1375.00 heavy smoker

NO
1371.00 Never smoked tobacco

EX
137s.00 ex smoker
1378.00 ex-light smoker
1379.00 ex moderate smoker
137K.00 stopped smoking

Unknown
None of these codes present

Ever asthma or COPD (any of these codes before index date)
173A.00 EXERCISE INDUCED ASTHMA
663..11 ASTHMA MONITORING
663N.00 ASTHMA DISTURBING SLEEP
663N000 ASTHMA CAUSING NIGHT WAKING
663N100 ASTHMA DISTURBS SLEEP WEEKLY
663N200 ASTHMA DISTURBS SLEEP FREQUENTLY
663O.00 ASTHMA NOT DISTURBING SLEEP
663O000 ASTHMA NEVER DISTURBS SLEEP
663P.00 ASTHMA LIMITING ACTIVITIES
663Q.00 ASTHMA NOT LIMITING ACTIVITIES
663U.00 ASTHMA MANAGEMENT PLAN GIVEN
663V.00 ASTHMA SEVERITY
663V000 OCCASIONAL ASTHMA
663V100 MILD ASTHMA
663V200 MODERATE ASTHMA
663V300 SEVERE ASTHMA
663W.00 ASTHMA PROPHYLACTIC MEDICATION USED
663d.00 EMERGENCY ASTHMA ADMISSION SINCE LAST APPOINTMENT
663e.00 ASTHMA RESTRICTS EXERCISE
663e000 ASTHMA SOMETIMES RESTRICTS EXERCISE
663e100 ASTHMA SEVERELY RESTRICTS EXERCISE
663f.00 ASTHMA NEVER RESTRICTS EXERCISE
663h.00 ASTHMA – CURRENTLY DORMANT
663j.00 ASTHMA – CURRENTLY ACTIVE
66YJ.00 asthma follow-up
66YK.00 asthma monitoring
66YE.00 asthma follow up
8793.00 ASTHMA CONTROL STEP 0
8794.00 ASTHMA CONTROL STEP 1
8795.00 ASTHMA CONTROL STEP 2
8796.00 ASTHMA CONTROL STEP 3
8797.00 ASTHMA CONTROL STEP 4
8798.00 ASTHMA CONTROL STEP 5
8H2P.00 EMERGENCY ADMISSION, ASTHMA
9OJ1.00 ATTENDS ASTHMA MONITORING
9OJ2.00 REFUSES ASTHMA MONITORING
9OJ3.00 ASTHMA MONITOR OFFER DEFAULT
9OJ4.00 ASTHMA MONITOR 1ST LETTER
9OJ5.00 ASTHMA MONITOR 2ND LETTER
9OJ6.00 ASTHMA MONITOR 3RD LETTER
9OJ7.00 ASTHMA MONITOR VERBAL INVITE
9OJ8.00 ASTHMA MONITOR PHONE INVITE
9OJ9.00 ASTHMA MONITORING DELETED
9OJA.00 ASTHMA MONITORING CHECK DONE
9OJA.11 ASTHMA MONITORED
9OJZ.00 ASTHMA MONITORING ADMIN.NOS
9Q21.00 PATIENT IN ASTHMA STUDY
H33..00 ASTHMA
H33..11 BRONCHIAL ASTHMA
H330.00 EXTRINSIC (ATOPIC) ASTHMA
H330.11 ALLERGIC ASTHMA
H330.12 CHILDHOOD ASTHMA
H330.13 HAY FEVER WITH ASTHMA
H330.14 POLLEN ASTHMA
H330000 EXTRINSIC ASTHMA WITHOUT STATUS ASTHMATICUS
H330011 HAY FEVER WITH ASTHMA
H330100 EXTRINSIC ASTHMA WITH STATUS ASTHMATICUS
H330111 EXTRINSIC ASTHMA WITH ASTHMA ATTACK
H330z00 EXTRINSIC ASTHMA NOS
H331.00 INTRINSIC ASTHMA
H331.11 LATE ONSET ASTHMA
H331000 INTRINSIC ASTHMA WITHOUT STATUS ASTHMATICUS
H331100 INTRINSIC ASTHMA WITH STATUS ASTHMATICUS
H331111 INTRINSIC ASTHMA WITH ASTHMA ATTACK
H331z00 INTRINSIC ASTHMA NOS
H332.00 MIXED ASTHMA
H333.00 ACUTE EXACERBATION OF ASTHMA
H33z.00 ASTHMA UNSPECIFIED
H33z000 STATUS ASTHMATICUS NOS
H33z011 SEVERE ASTHMA ATTACK
H33z100 ASTHMA ATTACK
H33z111 ASTHMA ATTACK NOS
H33z200 LATE-ONSET ASTHMA
H33zz00 ASTHMA NOS
H33zz11 EXERCISE INDUCED ASTHMA
H33zz12 ALLERGIC ASTHMA NEC
H33zz13 ALLERGIC BRONCHITIS NEC

H35y700 WOOD ASTHMA
H47y000 DETERGENT ASTHMA
H30.12 RECURRENT WHEEZY BRONCHITIS
H302.00 WHEEZY BRONCHITIS
H312000 CHRONIC ASTHMATIC BRONCHITIS
H312011 CHRONIC WHEEZY BRONCHITIS
8791.00 Further asthma – drug prevent. 11
TJF7300 Adverse reaction to theophylline (asthma) 53
TJF7.00 Adverse reaction to antiasthmatics 2
TJF7z00 Adverse reaction to antiasthmatic NOS 1
U60F615 [X] Adverse reaction to theophylline asthma 3
14B4.00 H/O: ASTHMA
H3...00 Chronic obstructive pulmonary disease
H3...11 Chronic obstructive airways disease
H36..00 Mild chronic obstructive pulmonary disease
H37..00 Moderate chronic obstructive pulmonary disease
H38..00 Severe chronic obstructive pulmonary disease
H39..00 Very severe chronic obstructive pulmonary disease
H3y..00 Other specified chronic obstructive airways disease
H3y..11 Other specified chronic obstructive pulmonary disease
H3z..00 Chronic obstructive airways disease NOS
H3z..11 Chronic obstructive pulmonary disease NOS
Hyu3100 [X]Other specified chronic obstructive pulmonary disease
H312100 Emphysematous bronchitis
H312.00 Obstructive chronic bronchitis
H312z00 Obstructive chronic bronchitis NOS
H312200 Acute exacerbation of chronic obstructive airways disease

Anti-depressant use or benzodiazepine use (past two years, code closest to index date)
ALPRAZOLAM
AMITRIPTYLINE AND BA
AMITRIPTYLINE HCL
AMOXAPINE
BROMAZEPAM
BUTRIPTYLINE
CHLORDIAZEPOXIDE W CLIDI
CHLORDIAZEPOXIDE HCL
CHLORDIAZEPOXIDE W AMITRIPTYLINE
CITALOPRAM
CLORAZEPATE DIPOTASSIUM
CLOBAZAM
CLOMIPRAMINE
CLONAZEPAM
DESVENLAFAXINE SUCCINATE
DIAZEPAM
DIBENZEPIN
DIBENZEPIN HCL
DOSULEPIN
DOTHIEPIN
DOXEPIN HCL
DULOXETINE HYDROCHLORIDE
ESCITALOPRAM OXALATE
FLUNITRAZEPAM
FLUOXETINE
FLURAZEPAM
FLUVOXAMINE
IMIPRAMINE HCL
IMIPRAMINE N-OXIDE HCL
IMIPRAMINE PAMOATE
IPRINDOLE
ISOCARBOXAZID
KETAZOLAM
LITHIUM CARBONATE
LITHIUM CITRATE
LOFEPRAMINE
LORAZEPAM
LORMETAZEPAM
MAPROTILINE HCL
MEDAZEPAM
MELITRACEN
MIANSERIN
MIDAZOLAM
MIRTAZAPINE
MOCLOBEMIDE
NEFAZODONE HCL
NITRAZEPAM
NOMIFENSINE MALEATE
NORTRIPTYLINE
NOXIPTYLINE
OPIPRAMOL HCL
OXAZEPAM
PAROXETINE
PHENELZINE SULFATE
PRAZEPAM
PROTRIPTYLINE HCL
REBOXETINE
SERTRALINE
ST JOHNS WORT
TEMAZEPAM
TOFENACIN
TRANYLCYPROMINE
TRANYLCYPROMINE PLUS AND MINUS ISOMERS
TRAZODONE HYDROCHLORIDE
TRIAZOLAM
TRIMIPRAMINE
TRYPTOPHAN
VENLAFAXINE
VILOXAZINE HCL
ZALEPLON
ZIMELIDINE
ZOLPIDEM
ZOPICIONE

References

[1] Health Protection Agency. Invasive pneumococcal disease (IPD) in England and Wales after 7-valent conjugate vaccine (PCV7): potential impact of 10- and 13-valent vaccine. http://www.hpa.org.uk/web/HPAwebfile/HPAweb_C/1245581527892 [accessed 01.07.12].
[2] Whitney CG, Farley MM, Hadler J, Harrison LH, Bennett NM, Lynfield R, et al. Decline in invasive pneumococcal disease after the introduction of protein polysaccharide conjugate vaccine. N Engl J Med 2003;348:1737–46.
[3] CDC. Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease – United States, 1998–2003. MMWR Morb Mortal Wkly Rep 2005;54:893–7.
[4] Gladstone RA, Jefferies JM, Faust SN, Clarke SC. Continued control of pneumococcal disease in the UK – the impact of vaccination. J Med Microbiol 2011;60:1–8.
[5] Miller E, Andrews NJ, Waight PA, Slack MP, George RC. Herd immunity and serotype replacement 4 years after seven-valent pneumococcal conjugate vaccination in England and Wales: an observational cohort study. Lancet Infect Dis 2011;11:780–6.
[6] Andrews N, Waight PA, Borrow R, Ladhani S, George RC, Slack MP, et al. Using the indirect cohort design to estimate the effectiveness of the seven valent pneumococcal conjugate vaccine in England and Wales. PLoS One 2011;6:e28435 [Epub ahead of print 2011 December 2].
[7] Hammitt LL, Bruden DL, Butler JC, Baggett HC, Hurlburt DA, Reasonover A, et al. Indirect effect of conjugate vaccine on adult carriage of *Streptococcus pneumoniae*: an explanation of trends in invasive pneumococcal disease. J Infect Dis 2006;193(June (11)):1487–94.
[8] van Gils EJM, Veenhoven RH, Hak E, Rodenburg GD, Bogaert D, Ijzerman EP, et al. Effect of reduced dose schedules with 7-valent pneumococcal conjugate vaccine on nasopharyngeal carriage in children: a randomized controlled trial. JAMA 2009;302:159–67.
[9] Flasche S, Van Hoek AJ, Sheasby E, Waight P, Andrews N, Sheppard S, et al. Effect of pneumococcal conjugate vaccination on serotype-specific carriage and invasive disease in England: a cross-sectional study. PLOS Med 2011;8:1–9.
[10] 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.
[11] Metlay JP, Lautenbach E, Li Y, Shults J, Edelestein PH. The changing role of exposure to children as a risk factor for bacteremic pneumococcal disease in the post conjugate area. Arch Intern Med 2010;170:725–31.
[12] Elston JW, Santaniello-Newton A, Meigh JA, Harmer D, Allgar V, Allison T, et al. Increasing incidence of invasive pneumococcal disease and pneumonia despite improved vaccination uptake: surveillance in Hull and East Yorkshire, UK, 2002–2009. Epidemiol Infect 2011;1:1–15.
[13] Jick H, Jick SS, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. BMJ 1991;302:766–8.
[14] Jick H, Terris BZ, Derby LE, Jick SS. Further validation of information recorded on a general practitioner based computerized data resource in the United Kingdom. Pharmacoepidemiol Drug Saf 1992;1:347–9.
[15] Jick SS, Kaye JA, Vasilakis-Scaramozza C, Garcia Rodríguez LA, Ruigómez A, Meier CR, et al. Validity of the general practice research database. Pharmacotherapy 2003;23:686–9.
[16] Schlienger RG, Fedson DS, Jick SS, Jick H, Meier CR. Statins and the risk of pneumonia: a population-based, nested case–control study. Pharmacotherapy 2007:325–32.
[17] Jick H, Hagberg KW. Effectiveness of influenza vaccination in the United kingdom, 1996–2007. Pharmacotherapy 2010;30:1199–206.

[18] Jick H, Hagberg KW. Measles in the United Kingdom 1990–2008 and the effectiveness of measles vaccines. Vaccine 2010;28:4588–92.
[19] Jick H, Chamberlin DP, Hagberg KW. The origin and spread of a mumps epidemic: United Kingdom, 2003–2006. Epidemiology 2009;20: 656–61.
[20] Shankar A, Samraj R, Aiyedun V, Janda M, Ramaiah S. General practitioners' perceptions on pneumococcal vaccination for children in United Kingdom. Hum Vaccine 2009;5:177–80.
[21] Vinogradova Y, Hippisley-Cox J, Coupland C. Identification of new risk factors for pneumonia: population-based case–control study. Br J Gen Pract 2009;59:e329–38.
[22] Hak E, Bont J, Hoes AW, Verheij TJ. Prognostic factors for serious morbidity and mortality from community-acquired lower respiratory tract infections among the elderly in primary care. Fam Pract 2005;22:375–80.
[23] Ardanuy C, Tubau F, Pallares R, Calatayud L, Dominquez MA, Rolo D, et al. Epidemiology of invasive pneumococcal disease among adult patients in Barcelona before and after pediatric 7-valent pneumococcal conjugate vaccine introduction, 1997–2007. Clin Infect Dis 2009;48:57–64.
[24] Jansen AG, Rodenburg GD, van der Ende A, van Alphen L, Veenhoven RH, Spanjaard L, et al. Invasive pneumococcal disease among adults: associations among serotypes, disease characteristics, and outcome. Clin Infect Dis 2009;49(July (2)):e23–9.
[25] NHS. NHS Immunisation Statistics England 2009–2010. The Health and Social Care Information Centre, Public health Indicators and Population Statistics Team; 2010.
[26] Amar RK, Jick SS, Rosenberg D, Maher TM, Meier CR. Incidence of the pneumoconioses in the United Kingdom general population between 1997 and 2008. Respiration 2012;84(3):200–6.