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Population-level impact of infant 10-valent pneumococcal conjugate vaccination on adult pneumonia hospitalisations, Finland

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Abstract

Introduction

Limited data are available on population-level herd effects of infant 10-valent Pneumococcal Conjugate Vaccine (PCV10) programmes on pneumonia. We assessed national trends in pneumococcal and all-cause pneumonia hospitalisations in adults ≥18 years, before and after infant PCV10 introduction in 2010.

Methods

Monthly hospitalisation rates of ICD-10 coded primary discharge diagnoses compatible with pneumonia from 2004-05 to 2014-15 were calculated with population denominators from the Population Register. Trends in pneumonia before and after PCV10 introduction were assessed with interrupted time-series analysis. Rates during the PCV10 period were estimated from adjusted negative binomial regression model and compared with those projected as continuation of the pre-PCV10 trend. All-cause hospitalisations were assessed for control purposes.

Results

Before PCV10, the all-cause pneumonia rate in adults ≥18 years increased annually by 2.4%, followed by a 4.7% annual decline during the PCV10 period. In 2014-15, the overall all-cause pneumonia hospitalisation rate was 109.3/100,000 (95% CI: 96.5, 121.9) - 15.4% lower than the expected rate. A significant 6.7% decline was seen in persons ≥65 years (131.5/100,000), which translates to 1456 fewer pneumonia hospitalisations annually. In comparison, hospitalisations other than pneumonia decreased by 3.5% annually throughout the entire study period.

Conclusion

These national data suggest that herd protection from infant PCV10 programme has reversed the increasing trend and substantially decreased all-cause pneumonia hospitalisations in adults, particularly the elderly.

Keywords:
Pneumonia hospitalisations, pneumococcal conjugate vaccine, herd effects

Summary Box

What is the key question?

In a nationwide, population-based study, we assessed whether vaccinating infants with the 10-valent pneumococcal conjugate vaccine (PCV10) had had an impact on adult pneumonia hospitalisations through herd protection.

What is the bottom line?

Although there was an increasing trend in rates of pneumonia before PCV10, five years after infant PCV10 introduction all-cause pneumonia hospitalisations had decreased significantly in all adult age groups, particularly the elderly.

Why read on?

In high-income countries, the ageing of population and the uncertain cost-effectiveness of preventing adult pneumococcal disease by direct vaccination highlight the public health significance of the pneumococcal conjugate vaccine programme's indirect impact in reducing the burden of adult pneumonia.

INTRODUCTION

Lower respiratory infections are the fourth common cause of death globally [1]. Community-acquired pneumonia (CAP) causes significant clinical and economic burden associated with hospitalisations, particularly in the elderly [2]. Recent estimates of the proportion of CAP that is attributable to *Streptococcus pneumoniae* (pneumococcus) in adults have ranged from 19% to 27%. However, because sensitive and specific assays are not routinely used in clinical practice – particularly for non-hospitalised cases – these estimates may be conservative [3, 4]. In a recent prospective cohort study of Finnish adults ≥65 years of age, CAP incidence was estimated to be 1050 cases/100,000 person-years; 17% of cases were due to *S. pneumoniae*, and 85% required hospitalisation [5]. In the U.S., the annual incidence of hospitalised CAP in adults ≥85 years of age was estimated to be >1600 cases/100,000 [6].

Pre-licensure clinical trials suggested a 20-40% effectiveness of the 7-valent pneumococcal conjugate vaccine (PCV7) against radiologically confirmed-pneumonia in children ≤ 5 years of age [7, 8]. In persons ≥65 years of age, one dose of the 13-valent pneumococcal conjugate vaccine (PCV13) reduced vaccine-serotype CAP by 45% in the Netherlands, but had little impact on overall pneumonia [9]. After introduction of PCV7 – and subsequently PCV13 – in routine infant immunization programmes, several population-based studies reported reductions in all-cause pneumonia hospitalisations in children [10, 11]. In Finland, PCV10 introduction was recently shown to have substantially decreased the incidence of pneumonia in both vaccine-eligible and older, unvaccinated children [12]. Infant PCV vaccination decreases carriage of vaccine-serotype pneumococci and, consequently, transmission to unvaccinated groups [13]. Few studies, however, have evaluated the population-level herd effects of infant PCVs on adult pneumonia hospitalisations [14–17]. Given the

increasing burden of pneumonia hospitalisations associated with ageing of the population, reducing morbidity and mortality from pneumonia in adults by infant pneumococcal vaccination would yield major public health benefits [18].

We conducted a nation-wide register-linkage study to assess the public health impact of infant PCV10 programme introduction on all-cause and pneumococcal pneumonia hospitalisations in adults ≥18 years of age in Finland.

METHODS

Pneumococcal vaccination in Finland

In September 2010, PCV10 was introduced in the Finnish National Vaccination Programme (NVP) under a 3-dose schedule (at 2, 5, and 12 months of age) without catch-up programme. All children born after June 2010 were eligible. In the 2012 birth cohort, the uptake of at least one dose of PCV10 was estimated to be 94% [19]. Use of the 23-valent pneumococcal polysaccharide vaccine (PPSV23) and PCV13 in adults at-risk and the elderly is recommended. However, there is no national adult vaccination program and in 2014 the cumulative coverage of both vaccines in adults was <5% on the basis of vaccine distribution data.

Study population and data sources

This was a nation-wide, population-based, quasi-experimental study. The national hospital discharge register includes discharge notifications for inpatient admissions and outpatient visits from all Finnish hospitals. ICD-10 coded discharge diagnoses and visit dates for pneumonia hospitalisations in all adults ≥18 years of age from 2004-05 to 2014-15 (epidemiologic years from July to June) were extracted; population denominators were from the population information system. Data were analysed in the following age groups: 18-49, 50-64, ≥65 and, ≥18 years of age. The age group ≥65 years was further divided into 65-74, 75-84, and ≥85 years of age.

Pneumonia definitions

All-cause pneumonia hospitalisation was defined as record of a patient hospitalised for at least overnight with ICD-10 coded pneumonia as the primary discharge diagnosis (J10-J18, and J86; Supplementary File: Tables 1 and 2). Pneumococcal pneumonia and empyema were defined as

patients with ICD-codes J13 and J86, respectively, in any discharge diagnosis field, with or without overnight hospitalisation. Potential multiple pneumonia discharge records for the same patient within 90 days from the date of the index pneumonia diagnosis were combined into one episode. The hospital discharge dataset included no radiological data. All-cause hospitalisations, defined as records of patients hospitalised for at least overnight with ICD-10 discharge codes other than J10-J18, and J86 were assessed for comparison.

Statistical analysis

Interrupted time-series analysis was used to compare rates of adult pneumonia before and after infant PCV10 introduction. The comparison periods for analysis included the pre-PCV10 period (epidemiologic years from 2004-05 to 2009-10; i.e. 72 monthly data points), and the PCV10 period (epidemiologic years from 2011-12 to 2014-15; i.e. 48 monthly data points); 2010-11 was considered a transitional period and excluded from the analysis.

Separate models were fitted for each case definition (all-cause pneumonia, pneumococcal pneumonia, empyema, and all-cause hospitalisations), age-group, and for the whole adult population. In all models, the outcome was the monthly number of episodes with the log of the population/100,000 as offset [20], and the reported measure was monthly incidence rate ratio, which was exponentiated to estimate the annual incidence rate ratio. The model parameters included the baseline rate at the beginning of the study and the trend before and after PCV10 introduction. Our model did not include the change in level as an immediate effect after the intervention because this is more relevant for studying the direct effect of PCVs on pneumonia hospitalisations in vaccine-eligible children [11]. In contrast, PCV-attributed herd protection in adults appears to have a “lag period” before coming into full effect [21] and in the absence of a clear definition of such lag period, setting

the time point for the change in level *a priori* would have been largely subjective. All models were adjusted for sex, and models for the aggregate age-groups were age-adjusted. To account for seasonal fluctuation in rates, all models included a Fourier seasonality component with the linear combinations of sine and cosine functions:

$$\log E(Y_t) = \log(C_t) + \beta_0 + \beta_1 T_t + \beta_2 X_t T_t + \beta_3 \sin[2\pi/12] + \beta_4 \cos[2\pi/12] + \beta_5 G_t$$

Where Y_t is the number of pneumonia episodes measured at month *t*. $\log(C_t)$ is the offset equal to the log of the population C_t divided by 100,000. β_0 is baseline rate. T_t is the time since the beginning of the study until month *t*, and β_1 is the pre-PCV10 slope. $X_t T_t$ is an interaction term and β_2 represents the post-PCV10 trend. The sine and cosine terms represent the Fourier seasonality component. G_t is a binary representing sex.

Trends in pneumonia episodes before and after PCV10 were compared by estimating annual incidence rate ratios (IRR) per 100,000 with the corresponding 95% confidence interval (CI). The IRR of the trend before-PCV10 is estimated as the change in annual hospitalisation rates from the first year in the observation period. The IRR of the trend after-PCV10 is estimated as the comparison of the annual trend in hospitalisation rate following the start of the PCV10 period to the period before. Percentage annual changes in trend were calculated as (IRR-1) x 100.

To quantify the indirect impact of PCV10, the rate at the end of the study period (i.e. epidemiologic year 2014-15) was estimated as the nonlinear prediction from the model with the full set of parameters, and was then compared with the expected rate that would have occurred in the absence of PCV10 introduction. The expected rates were nonlinearly predicted as continuation of the trend in the period before PCV10, by holding the model parameter denoting the trend after PCV10 at zero

[22]. The number of prevented pneumonia admissions per year was estimated by multiplying the annual absolute rate reduction by the population size in 2014-15. To smoothen the seasonal variation in the graphical presentation, symmetrical twelve-month moving average filters were applied to average monthly estimated and expected rates. Incidence rate residual analysis was done, including tests for autocorrelation and partial autocorrelations. These indicated no significant deviances from model assumptions. The level of statistically significant, two-tailed p-value was <0.05. Stata/SE version 14 (Stata, College Station, Texas, USA) was used in statistical analyses. The study protocol was approved by the institutional review board (IRB) in the National Institute for Health and Welfare (THL), Finland. Permissions to use the register data for research were obtained from the register controller at THL.

RESULTS

Characteristics of pneumonia hospitalisations

During the study period (2004-04 to 2014-15), >21.7 million hospital discharges were recorded in Finnish adults ≥18 years of age; 263,382 (1.2%) were all-cause pneumonia hospitalisation episodes. Pneumococcal pneumonia and empyema accounted for 1.8% and 1.1% of pneumonia episodes, respectively (Table 1). The baseline rate of and number of all-cause pneumonia hospitalisations in 2004-05 were 502.8/100,000 and 20,823, respectively (Table 2). The baseline rates ranged from 167.9/100,000 in persons 18-49 years of age to 4434.3/100,000 in those ≥85 years of age. The overall baseline rates for pneumococcal pneumonia and empyema were low (9.1 and 4.8/100,000, respectively).

Trends in pneumonia rates during the pre-PCV10 period

From July 2004 to June 2010, the rates of all-cause pneumonia hospitalisations in adults ≥18 years of age increased by 2.4% annually (incidence rate-ratio [IRR] 1.024; 95% CI: 1.018, 1.037) (Table 2). Similarly, rates of both pneumococcal pneumonia and empyema increased annually by 3.7% and 6.2% (IRRs 1.037 and 1.062, respectively). Age-stratified trend analysis showed increases in rates of all-cause pneumonia hospitalisations during the pre-PCV10 period in all age groups (Table 2).

Trends in pneumonia rates during the PCV10 period

From July 2011 to June 2015, the all-cause pneumonia rates in adults ≥18 years of age decreased annually by 4.7% (IRR 0.953; 95% CI: 0.942, 0.965) (Table 2). Statistically significant declines were seen in all age-specific rates except for adults ≥75 years of age; the largest reduction was seen in age groups 18-49 and 50-64 years (9.2%). The rate of pneumococcal pneumonia decreased annually by

8.1% (IRR 0.919; 95% CI: 0.876, 0.965); significant annual declines of 14.5% were seen in adults <65 years of age. Reductions in empyema rates were non-significant (Table 2).

Potential outcomes analysis

In epidemiologic year 2014-15, the estimated annual rate of all-cause pneumonia hospitalisations in adults ≥18 years of age was 109.3 episodes/100,000 (95% CI: 96.5, 121.9) or 15.4% lower compared with the expected rate on the basis of pre-PCV10 trends (Table 3, Figure 1a). For pneumococcal pneumonia, the overall rate reduction in 2014 was estimated to be 3.5 episodes per 100,000 (95% CI: 2.5, 4.4), or 26.5%. By 2014-15, the overall reduction in empyema was 1.5 episodes/100,000 (95% CI: 0.9, 2.1) (Table 3).

In age-stratified analyses, statistically significant reductions in all-cause pneumonia hospitalisations were seen in all age groups (Table 3, Figure 2). Compared with the expected rate, the estimated reductions in all-cause pneumonia hospitalisations in age-groups 18-49, 50-64, and ≥65 years were 44.1 (26.9%), 140.6 (28.8%), and 131.5 (6.7%) per 100,000 person-years, respectively. The greatest absolute reduction was seen in persons ≥85 years (195.9/100,000). During 2014-15, there were a total of 20,506 pneumonia hospitalisations among the 1,107,240 persons ≥65 years of age; the estimated rate decrease translates to 1456 fewer pneumonia hospitalisations in this age-group. Likewise, the estimated rate decreases in age-groups 18-49 (population, 2,180,022) and 50-64 (population, 1,117,998) translate to 961 and 1572 fewer pneumonia hospitalisations in 2014-15, respectively. Persons <65years of age had an estimated 41% reduction in pneumococcal pneumonia. Similar percent reduction was seen in persons ≥85 years of age, with the greatest absolute reduction in pneumococcal pneumonia rates (13.0 episodes/100,000). In persons 75-84 years of age, however, the

estimated rates were higher than expected by 5.4 episodes/100,000. By the end of the study period, the overall and age-stratified rates of empyema were significantly lower than expected, except for the youngest and the oldest age groups (Table 3).

Control condition: trends in all-cause hospitalisations

Before PCV10 introduction, all-cause hospitalisations (excluding pneumonia) decreased annually by 3.5% (IRR 0.965; 95% CI: 0.953, 0.976). The trend continued during the PCV10 period (Supplementary File: Figure 1).

DISCUSSION

This study provides evidence of herd effects and population-level impact of an infant PCV10 programme on adult pneumonia hospitalisations in a high vaccine uptake setting. The analysis of trends and potential outcomes showed an increasing pre-vaccine trend in adult pneumonia hospitalisations, followed by significant declines in overall- and age-stratified rates after PCV10 introduction. By 2014-15, the rate of all-cause pneumonia hospitalisations in adults had declined by 15% or 109 episodes per 100,000 population. Our data highlight both the substantial burden and opportunities for prevention of pneumonia in the elderly: Reductions in all-cause pneumonia hospitalisations in persons ≥65 years of age indicated about 1500 fewer annual hospitalisations.

During the period before PCV10, rates of pneumonia admissions in adults ≥18 years of age increased by 2.4% annually. Greater rate increases were seen in hospitalisations in which the presumptive aetiology was reported; as the overall rates of pneumococcal pneumonia and empyema increased by 3.7 and 6% annually. Increasing trends in adult pneumonia admissions were seen in England during 1997-2005, in Denmark during 1994-2004, and in the US during 1988-2002 (i.e. mostly before introduction of infant PCV7 programmes in these countries) [23-25]. The long-term increasing trend in pneumonia hospitalisations may be associated with ageing of the population and increase in the prevalence of underlying medical conditions, both recognized risk factors for CAP [26]. The proportion of elderly hospitalised pneumonia cases who had underlying medical conditions increased in the US during 1988-2002 [25]. In the UK, however, an increase in pneumonia admissions in the elderly during 1998-2010 was independent of increases in comorbidities, and was postulated to be associated with changes in service provision and health seeking behavior [27]. From 1996-2009, the number of pneumonia hospitalisations in Finland increased by 42%, primarily in the elderly; the duration of

hospital stay, however, decreased [28]. Changes in coding practices may also be associated with increases in pneumonia hospitalisations, but this is unlikely to have influenced our findings because we used only the primary discharge diagnosis and included all pneumonia-related ICD-10 codes in the analysis. We conducted an additional analysis of all episodes in which ICD-10 coded pneumonia was listed in any position of the discharge diagnoses, with or without hospitalisation. The relative reductions in pneumonia where similar to the analysis in which the case definition was restricted to the primary discharge diagnosis, but the absolute reductions were larger (Supplementary Tables 1 and 2).

Our trend analysis showed significant declines in rates of all-cause pneumonia hospitalisations following PCV10 introduction. In persons ≥65 years of age, the estimated annual decline was 2.4%, and in those 18-49 and 50-64 years of age it was 9.2%. In younger adults, rates of pneumococcal pneumonia also decreased. The large burden of all-cause pneumonia hospitalisations in persons ≥85 years of age, however, was associated with the greatest absolute reduction, an estimated 195.9 fewer episodes per 100,000 than expected – i.e. had the increasing pre-PCV10 trend continued. Population-based prospective surveillance studies have consistently reported that rates of CAP hospitalisations increase with advancing age [2, 5]. Pneumonia hospitalisations were previously projected to increase by 49% from 2010 to 2030 in Finland [28]. Percentage reductions in all-cause pneumonia hospitalisations by 2015, however, were greatest in young adults (26.9% in adults 18-49 years of age), which might be associated with reduced exposure to PCV10-serotypes in parents of vaccinated children. Although previous studies evaluating the impact of infant PCV7 programmes on adult pneumonia hospitalisations have consistently showed declines in pneumococcal pneumonia, the reported changes in age-specific all-cause pneumonia hospitalisation rates have varied across settings

[15, 17]. This variation could be associated with several factors or their combination, including differences in infant vaccination programmes (e.g. uptake, schedule, or catch-up), population characteristics, coding practices, admission criteria, or analytical methods.

Some limitations should be considered when interpreting the findings. First, the study design was ecological. Although our study aimed to estimate the indirect effect of infant PCV10, other adult vaccines, such as influenza, PCV13, and the 23-valent pneumococcal polysaccharide vaccine (PPSV23), may also decrease the risk of pneumonia hospitalisation. In Finland, influenza vaccination has been recommended for all persons ≥65 years of age since 2002. During our study period, the annual vaccine coverage has varied from 38% to 50%. Uptake was highest during the 2009 influenza pandemic, but actually decreased in subsequent years, i.e. during PCV10 period. In 2014, the cumulative coverage of PPSV23 and PCV13 in adults was <5% based on vaccine distribution data. This low coverage would not be expected to have a population-level impact on overall pneumonia incidence.

Second, all-cause pneumonia is a non-specific outcome and trends in other respiratory pathogens may influence its occurrence. In 2010-11, an increase in all-cause pneumonia was observed. Although this coincided with an epidemic of Mycoplasma pneumoniae infections in Finland, it is unlikely to have influenced our findings as most cases were in younger age groups (5-19 years of age) and the period (late-2010 to mid-2011) was excluded from our analysis [29]. In our study, some 95% of episodes were recorded as pneumonia due to unspecified cause, indicating the lack of sensitive and specific etiological diagnosis for pneumonia in a routine hospital care [3, 4]. To capture all episodes of pneumococcal pneumonia and empyema, we used broader case definition (with or without overnight hospitalisations) and also included non-primary discharge diagnoses. Nevertheless, these outcomes

accounted for <2% of pneumonia episodes in our study. In previous reports, laboratory-confirmed pneumococcal pneumonia accounted for a small fraction of all-cause pneumonia hospitalisations [15–17]. In addition, our sensitivity analysis showed no significant changes in pneumonia hospitalisations due to specified pathogens other than *S. pneumoniae* (data not shown). Our case definition also included healthcare-associated pneumonia, which is difficult to distinguish from community-acquired pneumonia in hospital discharge records and is mainly caused by bacteria other than *S. pneumoniae*.

Third, administrative data are subject to misclassification, secular changes in coding and clinical practices, as well as criteria for admission [30]. However, an Australian validation study estimated 98% sensitivity, 97% specificity, 96% positive predictive value, and 98% negative predictive value for ICD-10 coded pneumonia hospitalisations [31]. In the U.S., comparison of IPD rates reported by active surveillance with those estimated using ICD-coded data showed similar temporal trends [10]. Changes in admission criteria might be associated with the observed changes in pneumonia hospitalisation rates, particularly if there was a shift to management of less severe cases in outpatient settings [32]. The Finnish guidelines for the management of CAP published in 2008 introduced criteria for identifying low risk patients who could be managed on outpatient basis [33]. We therefore conducted a sensitivity analysis which showed that pneumonia hospitalisations continued to increase after the guidelines were published, and began to decrease only during the PCV10 period (Supplementary File: Figure 2). However, trends in outpatient visits for CAP could not be examined, as the outpatient register was established only after PCV10 introduction. The results of an additional analysis, which also included outpatient and emergency room pneumonia episodes, were similar to the analysis restricted to hospitalised episodes (Supplementary Tables 1 and 2). It is possible that the decreasing trend in hospitalisations other than pneumonia might be associated with a shift towards outpatient

management of various conditions, but this is unlikely to have influenced the observed trends in all-cause pneumonia hospitalisations.

Last, increases in chronic medical conditions which increase the risk of pneumococcal pneumonia also contribute to the disease burden. We could not assess the potential effect of underlying conditions in this study due to the complexity of obtaining comprehensive data on these conditions. Assessing whether indirect vaccine effects against pneumonia are different in persons with and without high risk conditions will help better defining the characteristics of herd protection in adults.

The strengths of this study included the use of comprehensive, nation-wide, population-based register data with a case definition for pneumonia hospitalisation with increased specificity of the main outcome, hospital-treated primary pneumonia. Although our dataset did not include radiological data, it is likely that our case definition captured most radiologically confirmed episodes as patients were hospitalised at least overnight and pneumonia was the primary discharge diagnosis. Our data enabled using interrupted time-series analysis with sufficient data points before and after infant PCV10 to estimate the herd effect on adult pneumonia hospitalisations. This analysis method had advantages over the two-point, before-after design because it incorporated multiple time points and enabled accounting for seasonal variation, and importantly, the pre-vaccine secular increase in pneumonia hospitalisations in Finland [28]. Last, our analysis showed the trends in all-cause hospitalisations or potential shifts in outpatient management of CAP were unlikely to explain the trends in pneumonia hospitalisations.

In conclusion, these national data suggest that herd protection from infant PCV10 has reversed the increasing trend and substantially decreased all-cause pneumonia hospitalisations in adults,

particularly in the elderly. This finding is significant as the number of persons ≥65 years of age in Finland is projected to increase by 17% from 2014 to 2020, likely increasing the burden of CAP hospitalisations even further [34]. The findings also have major implications for economic analyses comparing strategies for prevention of pneumococcal diseases in adults.

Tables

Table 1. Hospitalisations for pneumonia episodes in adults ≥18 years of age, Finland, epidemiologic years from 2004-05 to 2014-15

Epidemiologic Years [a]	**Total Population ≥18 years of age**	**Pneumonia episodes** [b]					
		All-cause pneumonia hospitalisations		**Empyema**		**Pneumococcal Pneumonia**	
		n	Rate per 100,000 population	*n*	Rate per 100,000 population	*n*	Rate per 100,000 population
2004-05	4141374	20823	502.8	198	4.8	377	9.1
2005-06	4164582	20542	493.3	179	4.3	338	8.1
2006-07	4190862	20821	496.8	197	4.7	402	9.6
2007-06	4219620	21082	499.6	237	5.6	395	9.4
2008-09	4248882	23640	556.4	264	6.2	516	12.1
2009-10	4276986	22394	523.6	264	6.2	449	10.5
2010-11	4305246	26744	621.2	273	6.3	437	10.2
2011-12	4333734	28609	660.2	294	6.8	441	10.2
2012-13	4361280	26376	604.8	291	6.7	469	10.8
2013-14	4385442	25189	574.4	309	7.0	447	10.2
2014-15	4405260	27162	616.6	307	7.0	407	9.2
Total	-	**263382**	-	**2813**	-	**4678**	-

[a] Years runs from July to June. [b] Potential multiple pneumonia discharge records for the same patient within 90 days from the date of the index pneumonia diagnosis were combined into one episode.

Table 2. Trends in hospitalisations for all-cause pneumonia, pneumococcal pneumonia, and empyema in adults ≥18 years of age before and after introduction of ten-valent pneumococcal conjugate vaccine (PCV10) in the national infant vaccination programme, Finland

Outcome	Baseline Rate in 2004-05 (per 100,000 population)	Adjusted annual trends using interrupted time-series analysis					
		Period before PCV10 (2004-05 to 2009-10[a])			Period after PCV10, (2011-12 to 2014-15[a])		
		Annual trend			Annual trend		
		IRR	95% CI	*P*[b]	IRR	95% CI	*P*[b]
All-cause pneumonia							
Age (years)							
18-49	167.9	1.012	0.988, 1.037	0.075	0.908	0.876, 0.953	<0.001
50-64	310.6	1.049	1.037, 1.062	<0.001	0.908	0.876, 0.930	<0.001
≥65[c]	1639.8	1.018	1.013, 1.023	<0.001	0.976	0.965, 0.988	0.004
65-74	816.7	1.024	1.012, 1.037	<0.001	0.965	0.942, 0.988	0.016
75-84	2071.8	1.012	1.007, 1.024	<0.001	0.976	0.965, 1.002	0.081
≥85	4434.3	1.024	1.012, 1.028	<0.001	0.988	0.965, 1.012	0.375
Total[c]	502.8	1.024	1.018, 1.037	<0.001	0.953	0.942, 0.965	<0.001
Pneumococcal pneumonia							
Age (years)							
18-49	5.7	1.037	1.002, 1.087	0.029	0.855	0.775, 0.953	0.003
50-64	10.4	1.062	1.024, 1.087	0.001	0.855	0.785, 0.930	<0.001
≥65[c]	16.3	1.012	0.988, 1.049	0.290	0.988	0.919, 1.062	0.845
65-74	11.3	1.037	0.988, 1.087	0.073	0.976	0.876, 1.074	0.604
75-84	20.9	0.988	0.942, 1.037	0.515	1.087	0.965, 1.224	0.186
≥85	25.6	1.024	0.953, 1.087	0.590	0.865	0.711, 1.037	0.105
Total[c]	9.1	1.037	1.012, 1.049	<0.001	0.919	0.876, 0.965	<0.001
Empyema							
Age (years)							
18-49	2.4	1.024	0.976, 1.062	0.378	0.976	0.865, 1.114	0.736
50-64	7.4	1.049	1.012, 1.087	0.015	0.930	0.844, 1.024	0.117
≥65[c]	7.7	1.100	1.062, 1.154	<0.001	0.919	0.844, 1.012	0.074

Outcome	Baseline Rate in 2004-05 (per 100,000 population)	Adjusted annual trends using interrupted time-series analysis					
		Period before PCV10 (2004-05 to 2009-10[a])			Period after PCV10, (2011-12 to 2014-15[a])		
		Annual trend			Annual trend		
		IRR	95% CI	*P*[b]	IRR	95% CI	*P*[b]
65-74	8.9	1.100	1.037, 1.154	<0.001	0.930	0.824, 1.049	0.248
75-84	4.7	1.114	1.049, 1.196	0.001	0.908	0.766, 1.074	0.266
≥85	11.7	1.114	1.012, 1.253	0.035	0.908	0.702, 1.168	0.435
Total[c]	4.8	1.062	1.037, 1.087	<0.001	0.942	0.897, 1.002	0.059

IRR: Incidence rate ratio. IRRs are adjusted for sex and seasonality, with the natural log of the population size as the offset variable. The IRR of the trend before-PCV10 is estimated as the change in annual hospitalisation rates in the years 2004-05 to 2009-10. The IRR of the trend after-PCV10 is estimated as the comparison of the annual trend in the years 2011-12 to 2013-14 to the trend in the period before .[a] PCV10 was introduced in the Finnish NVP in September 2010. The year 2010-11 was defined as a transitional period and was excluded from the analysis. [b] Two-tailed *P* value. [c] Analyses for the aggregate age-groups (i.e. the total [≥18 years of age] and the ≥65 years of age) were age-adjusted using the following age groups: all age groups in the analyses for the total, and the 65-74, 75-84, and ≥85 years of age in the analyses for the ≥65 years of age group.

Table 3. Estimated and expected hospitalisation rates of all-cause pneumonia in adults ≥18 Years of age, 2014-15

Outcome	Estimated rate per 100,000 population [a]	Expected rate per 100,000 population [b]	Expected versus estimated hospitalisation rates in 2014-15		
			Rate difference per 100,000 population	95% CI [c] per 100,000 population	Percent reduction (%)
All-cause pneumonia					
Age (years)					
18-49	120.1	164.2	44.1	35.3, 52.9	26.9
50-64	348.8	488.8	140.6	122.1, 158.9.0	28.8
≥65 [d]	1820.4	1951.9	131.5	106.0, 156.9	6.7
65-74	869.3	968.4	99.1	73.1, 125.0	10.2
75-84	2260.5	2417.3	156.8	106.7, 206.9	6.5
≥85	5097.5	5293.3	195.9	77.3, 314.4	3.7
Total [d]	598.8	708.0	109.3	96.5, 121.9	15.4
Pneumococcal pneumonia					
Age (years)					
18-49	4.6	7.9	3.3	1.9, 4.6	41.7
50-64	10.0	17.1	7.1	4.7, 9.5	41.4
≥65 [d]	18.9	19.4	0.5	-0.9, 1.9	2.5
65-74	17.4	19.1	1.7	-0.7, 4.2	9.1
75-84	21.7	16.3	-5.4	-5.9, -4.8	-33.0
≥85	18.9	31.9	13.0	3.4, 22.6	40.6
Total [d]	9.5	12.9	3.5	2.5, 4.4	26.5
Empyema					
Age (years)					
18-49	2.8	3.0	0.2	-0.1, 0.6	7.0
50-64	8.5	11.1	2.6	1.2, 4.0	23.4
≥65 [d]	13.8	18.4	4.6	1.9, 7.2	24.9
65-74	13.4	17.3	3.8	0.5, 7.1	22.2
75-84	13.8	19.1	5.3	0.2, 10.4	27.8
≥85	15.9	22.5	6.6	-3.3, 16.4	29.2
Total [d]	7.0	8.5	1.5	0.9, 2.1	17.5

[a] Estimated rate is the average hospitalisation rate estimated from the adjusted negative binomial regression model, which included as independent variables the time since the beginning of the study and time since the start of the intervention period. The year 2010-11 was considered a transitional period and excluded from the analysis. [b] Expected rate is the average hospitalisation rate estimated from the adjusted model with the time since the beginning of the study as the independent variable. [c] 95% Confidence Intervals are estimated using Delta method, and were considered significant if they did not include zero. [d] Analyses for the aggregate age-groups (i.e. the total [≥18 years of age] and the ≥65 years of age) were age-adjusted using the following age groups: all age groups in the analyses for the total, and the 65-74, 75-84, and ≥85 years of age in the analyses for the ≥65 years of age group.

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Competing interests

Authors OO and JPN: no conflict of interest. Authors HRK, ER, AP, HN, and JJ are employees of the National Institute for Health and Welfare, Department of Health Protection, which has received research funding from GlaxoSmithKline for a Nation-wide effectiveness trial of the ten-valent pneumococcal conjugate vaccine. HRK, AAP, ER, and JJ are coinvestigators in the trial.

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Authors' contributions

Study concept and design: Okasha, Palmu, Jokinen and Nuorti. Acquisition of data: Rinta-Kokko and Ruokokoski. Analysis and interpretation of data: Okasha, Rinta-Kokko, Palmu, Jokinen, and Nuorti.

Drafting of the manuscript: Okasha and Nuorti. Critical revision of the manuscript for important intellectual content: Okasha, Rinta-Kokko, Palmu, Nohynek, Jokinen, and Nuorti. Statistical analysis: Okasha and Rinta-Kokko. Obtained funding: Nuorti. Study supervision: Nuorti. Final approval: Okasha, Rinta-Kokko, Palmu, Ruokokoski, Nohynek, Jokinen, and Nuorti.

Legend (Figure 1 and 2)

The vertical black dash-dot line marks to the introduction of PCV10 in the Finnish National Vaccination Programme. The period between the vertical red dash lines, i.e. July 2010 to June 2011, is a transitional period and was excluded from the analysis. Observed rate is the unadjusted average monthly hospitalisation rate. Estimated rate is the average hospitalisation rate estimated from the adjusted negative binomial regression model with the full set of parameters (i.e. time since the beginning of the study and time since the start of the intervention period). Expected rate is the average rate estimated from the model with time since the beginning of the study as the only independent variable. 12-month moving average filter was applied to both estimated and expected rates.

Figure 1

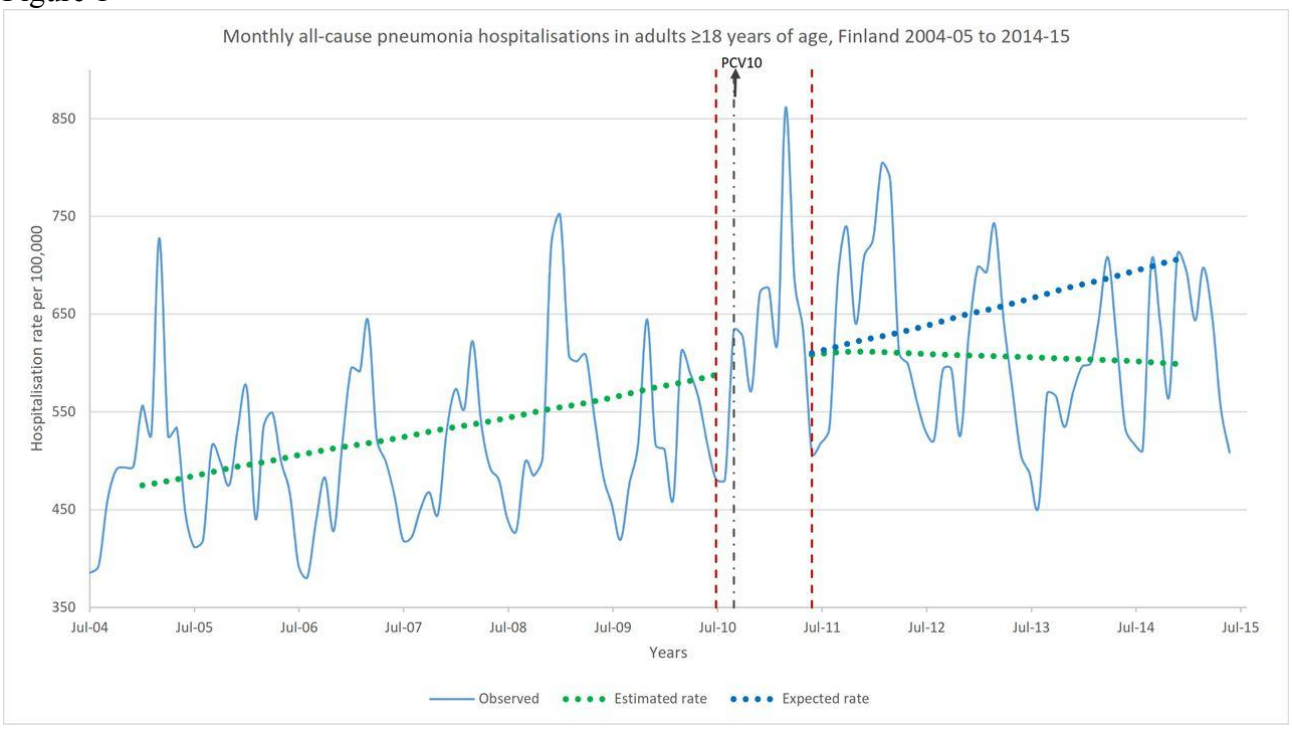

Figure 2