



Long-term population effects of infant 10-valent pneumococcal conjugate vaccination on pneumococcal meningitis in Finland



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ABSTRACT

Background: No previous studies have reported long-term follow-up of ten-valent pneumococcal conjugate vaccine (PCV10) program impact on pneumococcal meningitis (PM). We assessed the effects of infant PCV10 program on PM incidence, mortality and serotype distribution in children and adults during 7 years after introduction.

Methods: We conducted a population-based observational study. A case of PM was defined as isolation of *Streptococcus pneumoniae* from cerebrospinal fluid or, a patient with *S. pneumoniae* isolated from blood and an ICD-10 hospital discharge diagnosis of bacterial meningitis within 30 days before or after positive culture date. We compared age- and serotype-specific incidence and associated 30-day mortality rates in 2011–2017 (PCV10 period) with those in 2004–2010 (pre-PCV10 baseline) by using Poisson regression models. Absolute rate differences and 95% confidence intervals (CIs) were calculated from the parameter estimates by using delta method.

Results: During the PCV10 period, the overall incidence of PCV10 serotype meningitis decreased by 68% (95%CI 57%–77%), and the overall PM incidence by 27% (95%CI: 12%–39%). In age groups 0–4, 50–64, and ≥ 18 years, the overall PM incidence was reduced by 64%, 34% and 19%, respectively. In adults ≥ 65 years of age, a 69% reduction in PCV10 serotypes was offset by 157% (56%–342%) increase in non-PCV10 serotypes. The overall PM-related mortality rate decreased by 42% (95%CI 4%–65%). Overall case fatality proportion (CFP) was 16% in pre-PCV10 period and 12% in PCV10 period ($p = 0.41$); among persons 50–64 years the CFP decreased from 25% to 10% ($p = 0.04$).

Conclusions: We observed substantial impact and herd protection for vaccine-serotype PM and associated mortality after infant PCV10 introduction. However, in older adults ≥ 65 years of age, PM burden remains unchanged due to serotype replacement.

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1. Introduction

Streptococcus pneumoniae remains a leading cause of bacterial meningitis worldwide [1]; an estimated 83 900 cases (36,100–169,000) of pneumococcal meningitis (PM) occurred in 2015 in children under 5 years of age [2]. It is the most severe form of invasive pneumococcal disease (IPD), characterized by 8% to 50% case-fatality and frequent long-term complications in survivors [3]. Approximately half of the cases suffer sequelae such as hearing loss, seizures and cognitive impairments [4,5]. Incidence rates are

highest in young children and the elderly, but the disease affects all age groups [6].

Decreases in PM incidence in children have been reported after introduction of 7-, 10- and 13-valent pneumococcal conjugate vaccines (PCV7, PCV10, PCV13) into infant immunization programs [7–15]. Many studies have also reported herd protection against PM in unvaccinated population groups, especially older adults. However, reductions in vaccine serotypes were often offset by increases in non-vaccine serotypes (serotype replacement) [16–19].

In September 2010, Finland introduced PCV10 in the National Vaccination Programme (NVP) with a 2 + 1 schedule (3, 5 and 12 months of age). PCV10 effectiveness against invasive pneumococcal disease (IPD) due to vaccine serotypes (VT IPD) in children was first demonstrated in a large cluster-randomized trial (FinIP)

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conducted in 2009–2012. For VT IPD and IPD irrespective of serotype, vaccine effectiveness was 100% and 93%, respectively [20]. A subsequent surveillance study conducted 3 years after PCV10 introduction, showed a reduction by 80% of overall IPD rate in vaccine-eligible children and 48% reduction in unvaccinated children 2 to 5 years of age [21]. The early estimate for relative rate reduction in PCV10-type meningitis cases was 69% (95%CI 10% to 93%). However, the point estimate for overall reduction in pneumococcal meningitis cases (46%) was not statistically significant (95%CI – 19% to 78%)[21]. In a long term follow-up study six years after vaccine introduction, the overall IPD incidence had decreased by 79% in vaccine-eligible children and 33% in unvaccinated, older children [22].

No previous studies have reported long-term follow-up of PCV10 impact on pneumococcal meningitis in children and adults. We assessed the population effects of the infant PCV10 program on pneumococcal meningitis incidence and mortality after 7 years of vaccine introduction in a national study.

2. Methods

2.1. Surveillance on pneumococcal meningitis

The Population Information System of Finland is an online database containing information on name, sex, date of birth, place of residence and vital status of about 5.5 million permanent residents. This database can be linked with other health care and surveillance registries by using personal identity code (PIC). Since 1995, all clinical microbiology laboratories are obliged by law to report isolation of *Streptococcus pneumoniae* or detection of *S. pneumoniae* nucleic acid in blood or cerebrospinal fluid (CSF) to the National Infectious Diseases Register (NIDR), a population-based electronic laboratory surveillance system, maintained by the Finnish Institute for Health and Welfare (THL)[23]. Multiple notifications of IPD with the same PIC are merged into single case, if they occurred within 3 months from the first report. All clinical microbiology laboratories are also obliged to submit *S. pneumoniae* isolates from reported cases to THL reference laboratory for species verification and characterization.

2.2. Laboratory methods

Until 2009, pneumococcal isolates were serotyped by latex agglutination and/or counterimmunoelectrophoresis supplemented with Quellung reaction. During 2010–2017, isolates were serotyped by sequential multiplex PCRs supplemented with Quellung reaction, if needed [24]. All serotype 6A isolates from 2004 to 2009 were re-tested to distinguish serotype 6C and 6D. Since 2010, serotype 6C and 6D identification have been done routinely. Serotyping results have been routinely linked with the surveillance database by using PIC since 2004.

2.3. Study design and data sources

We conducted a population-based observational before-after study. Culture confirmed cases reported to NIDR with date of sampling from July 1, 2004 to June 30, 2017 were included in the analysis. The pre-PCV10 baseline period was defined as time-period from July 1, 2004 to June 30, 2010, and PCV10-period as time-period from July 1, 2011 to June 30, 2017. We excluded the transition year from July 1, 2010 to June 30, 2011. The case's vital status within 30 days from the first positive CSF or blood culture was obtained from The Population Information System. Cause of death data were not available. Data on discharge diagnoses were

obtained from the national hospital discharge register (the Care Register for Health Care at THL).

2.4. Case definitions

A case of PM was defined as isolation of *S. pneumoniae* from CSF or a patient with *S. pneumoniae* isolated from blood and an ICD-10 hospital discharge diagnosis G00.0, G.001, G.002 or G00.9 within 30 days before or after collection of culture positive specimen.

Cases were categorized into five groups according to the causative serotypes: PCV10 serotype PM (1, 4, 5, 6B, 7F, 9 V, 14, 18C, 19F, 23F), PCV13 serotype PM (PCV10 + 3, 6A, 19A), PM caused by serotypes unique to the 23-valent pneumococcal polysaccharide vaccine (PPSV23) (2, 8, 9 N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F), non-vaccine type PM (NVT; serotypes not included in PCV10, PCV13, PPSV23 vaccines), and any culture-confirmed PM.

Because other studies have shown increases or inconclusive results related to serotypes 3, 6A, 6C, 19A, 22F after PCV introduction, cases of these serotypes were analyzed separately.

2.5. Statistical analysis

We calculated total and serotype-specific incidence rates, related 30-day mortality rates and case fatality proportions of PM overall and in specific age groups (0–4 years; 5–17 years; 18–49 years; 50–64 years; ≥65 years; ≥18 years) during the study periods. Data from The Population Information System were used as denominators. The case fatality proportion (CFP) was defined as number of cases resulting in death within 30 days from the first positive culture divided by all cases. To assess changes in CFP, we used chi-square test. Statistical significance was deemed at the 5% level.

Comparisons of PM incidence and mortality rates between pre-PCV10 baseline and PCV10-periods were performed by using Poisson regression models. Absolute rate differences and their 95% CIs were calculated from the parameter estimates by using delta method. Relative rate reduction (RRR) was defined as $(1 - \text{incidence rate ratio}) \times 100\%$, comparing the pre-PCV10 baseline period and PCV10-period. All analyses were conducted with R version 3.4.2 and MS Excel 2013.

To assess changes in serotype distribution we compared the proportions of vaccine serotype groups in the pre-PCV10 period and in the final epidemiological year of the study (July 1, 2016 – June 30, 2017).

2.6. Ethical considerations

Data used in the study were de-identified and permission to use the register data for research was obtained from the relevant register controllers at THL (THL/1090/6.02.00/2013). THL Institutional Review Board approved the study.

3. Results

3.1. Changes in pneumococcal meningitis incidence rates

3.1.1. Overall incidence rates

A total of 451 culture-confirmed PM cases were reported during the study period (median age 57 years, IQR 40–66 years). Of the cases, 257 occurred during the pre-PCV10 baseline period and 194 during PCV10 period. The overall annual incidence rate varied from 1.07 cases per 100,000 person-years in 2008–2009 to 0.44 in 2016–2017 (Fig. 1). During the pre-PCV10 period and PCV10-period, 28% and 30% of cases were identified based on positive blood culture and ICD10-coded bacterial meningitis discharge

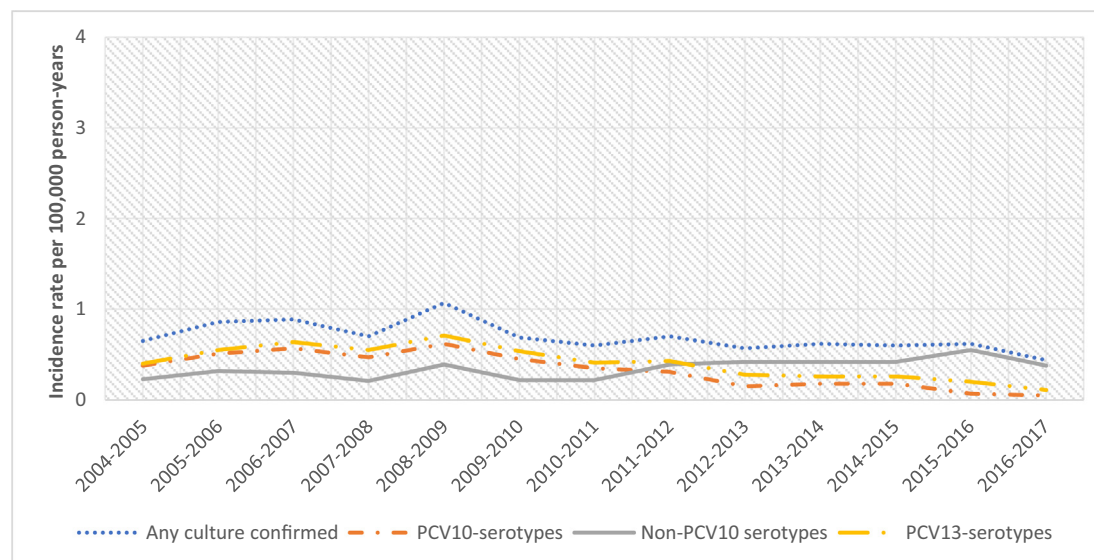


Fig. 1. Annual pneumococcal meningitis incidence rate per 100,000 person-years, according to the causing serotype, 2004–2017, Finland.

diagnosis, respectively; the rest of the PM cases were identified based on positive CSF culture. The overall PM incidence rate decreased by 27% from 0.81 cases during pre-PCV10 period to 0.59 cases per 100,000 person-years in the PCV10 period (IRR 0.73; 95%CI: 0.61–0.88). Compared with the baseline period, incidence decreased by 64% in children 0–4 years of age (IRR 0.36, 95%CI 0.19–0.63) and by 34% in adults 50–64 years of age (IRR 0.66, 95%CI 0.47–0.90). In all adults ≥ 18 years of age, the PM incidence rate decreased by 19% from 0.82 cases to 0.67 cases per 100,000 person-years (IRR 0.81; 95%CI 0.66–0.99). In other age groups, the point estimates decreased, but confidence intervals included one (Table 1).

3.1.2. Serotype-specific incidence rates

Compared with the pre-PCV10 baseline period the incidence of meningitis caused by PCV10 serotypes decreased by 68%, from 0.50 to 0.16 cases per 100,000 person-years (Table 1). In children 0–4 years of age, the incidence rate of PCV10-serotype PM decreased by 87% from 2.07 to 0.28 cases per 100,000 person-years. In adults 18–49 and 50–64 years of age the rates decreased by 63%, from 0.27 to 0.10 cases per 100,000 person-years and by 63% from 0.68 to 0.25 cases per 100,000 person-years, respectively. Among adults ≥ 65 years of age the incidence rate of PCV10-serotype PM decreased by 69%, from 0.71 to 0.22 cases per 100,000 person-years. In all these four age groups, the incidence of PM caused by PCV13-serotypes also decreased (Table 1). Overall incidence of non-PCV10 serotype PM increased by 54% from 0.28 to 0.43 cases per 100,000 person-years. This was mainly due to increase by 157% in adults ≥ 65 years of age, from 0.36 cases in pre-PCV10 period to 0.94 cases per 100,000 person-years in PCV10-period. Overall incidence of non-PCV13 serotypes increased by 57% from 0.21 to 0.34 cases per 100,000, primarily due to increases in children 0–4 years of age and adults ≥ 65 years of age (Table 1). Supplement Fig. 1 shows annual incidence rates by age group. In the whole population, the incidence of serotypes 19A and 6C PM increased, but the absolute rate differences were small (0.03 and 0.04 cases per 100,000 person-years, respectively). PM caused by serotypes 3 and 6A did not change in any age group. PM caused by the three serotypes in PCV13 but not in PCV10 (3, 6A, 19A) increased in adults 18–49 years, but the absolute rate change was minimal (0.04/100,000). Table 1 shows the detailed data on changes in serotype-specific incidence rates.

In adults ≥ 18 years of age, incidence of PCV10 and PCV13 serotype PM decreased by 64% from 0.47 to 0.17 cases per 100,000 person-years and by 47% from 0.54 to 0.28 cases per 100,000 person-years, respectively. Incidence of non-PCV10 PM increased by 54%, but the absolute rate change was small. This was primarily due to increase in serotype 6C from 0.01 to 0.05 cases per 100,000 person-years, and 19A from 0.004 to 0.05 cases per 100,000 person-years. Rates of meningitis caused by PPSV23 unique serotypes were 0.13 and 0.18 cases per 100,000 person-years during pre-PCV10 and PCV10 periods, respectively. In adults ≥ 65 years of age, the incidence rate of PPSV23 unique serotypes increased from 0.13 to 0.33 cases per 100,000 person-years.

3.1.3. Changes in serotype distribution

By the final epidemiological year of the study (2016–2017), the proportion of PCV10 serotypes had reduced from 88%, 56% and 66% of all isolates in pre-PCV10 period to 0%, in persons 0–4 years, 5–17 years and 18–49 years of age, respectively (Fig. 2). The proportion of meningitis caused by PCV13-PCV10 serotypes decreased in persons 0–4 years (from 5% to 0%), 5–17 years (from 22% to 0%) and 50–64 years of age (from 10% to 0%). In adults 18–49 years of age and ≥ 65 years of age the proportion of PCV13-PCV10 serotypes increased from 2% to 50% and from 12% to 14%, respectively.

The proportion of PPSV23 unique serotypes dropped in adolescents 5–17 years of age and adults 18–49 years of age from 11% and 15% of all isolates to 0% in the last epidemiological year, respectively. The proportion of PPSV23 unique serotypes increased in persons 50–64 years of age (from 19% to 50%) and in people ≥ 65 years of age (from 12% to 43%). In persons 50–64 years of age, the proportion of NVT serotype PM had decreased from 22% to 17%. In adults ≥ 65 years of age, the proportion of NVT PM increased from 16% to 36% (Fig. 2).

In adults ≥ 18 years of age, comparing 2016–2017 to the pre-PCV10 period, the proportion of PCV10 serotypes decreased from 57% to 14%. On the contrary, there was an increase from 16% to 41% in proportion of PPSV23 unique serotypes. The proportion of NVT serotypes increased from 19% in pre-PCV10 to 41% in 2016–2017 (Fig. 2).

In 2016–2017, the serotypes causing most cases were 22F, 6C and 23A (Fig. 3). Compared with the pre-PCV10 period, these serotypes also had the largest increases (Fig. 3).

Table 1

Incidence rates of pneumococcal meningitis (PM) and the corresponding relative and absolute rate reduction according to age group, based on the comparison of the pre-PCV10 period vs PCV10 period, Finland.

	Age group (years)	Pre-PCV10 period Incidence rate per 100,000 person-years (N)	PCV10 period Incidence rate per 100,000 person-years (N)	PCV10 period vs. Pre-PCV10 period		
				Incidence rate ratio	Relative rate reduction (%)	Absolute rate reduction/100,000 person-years
Any culture confirmed PM						
	0–4	2.35 (41)	0.84 (15)	0.36 (0.19, 0.63)	64.45 (37.21, 80.94)	1.52 (0.68, 2.35)
	5–17	0.19 (9)	0.09 (4)	0.46 (0.13, 1.42)	53.86 (–41.69, 87.5)	0.1 (–0.05, 0.25)
	18–49	0.40 (53)	0.31 (40)	0.76 (0.50, 1.14)	24.05 (–14.22, 49.89)	0.1 (–0.05, 0.24)
	50–64	1.38 (93)	0.90 (61)	0.66 (0.47, 0.90)	34.46 (9.74, 52.75)	0.47 (0.11, 0.83)
	≥65	1.17 (61)	1.15 (74)	0.99 (0.70, 1.39)	1.37 (–38.79, 29.65)	0.02 (–0.38, 0.41)
	All*	0.81 (257)	0.59 (194)	0.73 (0.61, 0.88)	26.81 (11.87, 39.31)	0.22 (0.09, 0.35)
PCV10-serotypes						
	0–4	2.07 (36)	0.28 (5)	0.14 (0.05, 0.31)	86.5 (68.64, 95.36)	1.79 (1.07, 2.51)
	5–17	0.10 (5)	0.06 (3)	0.62 (0.13, 2.54)	37.71 (–153.87, 87.22)	0.04 (–0.08, 0.16)
	18–49	0.27 (35)	0.10 (13)	0.37 (0.19, 0.69)	62.62 (31.13, 80.94)	0.17 (0.06, 0.27)
	50–64	0.68 (46)	0.25 (17)	0.37 (0.21, 0.63)	63.07 (36.87, 79.41)	0.43 (0.2, 0.66)
	≥65	0.71 (37)	0.22 (14)	0.31 (0.16, 0.56)	69.24 (44.42, 83.92)	0.49 (0.24, 0.75)
	All	0.50 (159)	0.16 (52)	0.32 (0.23, 0.43)	68.29 (56.96, 77.02)	0.34 (0.25, 0.43)
Non-PCV10 serotypes						
	0–4	0.23 (4)	0.56 (10)	2.43 (0.81, 8.86)	–142.94 (–785.68, 18.74)	–0.33 (–0.74, 0.08)
	5–17	0.08 (4)	0.02 (1)	0.26 (0.01, 1.75)	74.05 (–75.45, 98.67)	0.06 (–0.03, 0.15)
	18–49	0.13 (17)	0.21 (27)	1.60 (0.88, 2.99)	–59.83 (–198.81, 12.06)	–0.08 (–0.18, 0.02)
	50–64	0.67 (45)	0.64 (43)	0.96 (0.63, 1.45)	4.51 (–45.16, 37.27)	0.03 (–0.24, 0.3)
	≥65	0.36 (19)	0.94 (60)	2.57 (1.56, 4.42)	–156.74 (–341.56, –56.36)	–0.57 (–0.86, –0.28)
	All	0.28 (89)	0.43 (141)	1.54 (1.18, 2.01)	–53.62 (–100.91, –18.08)	–0.15 (–0.24, –0.06)
PCV13-serotypes						
	0–4	2.18 (38)	0.34 (6)	0.15 (0.06, 0.34)	84.66 (66.35, 94.17)	1.85 (1.1, 2.59)
	5–17	0.15 (7)	0.06 (3)	0.45 (0.10, 1.6)	55.51 (–60.04, 90.41)	0.08 (–0.05, 0.21)
	18–49	0.27 (36)	0.15 (19)	0.53 (0.30, 0.91)	46.89 (8.54, 70.13)	0.13 (0.02, 0.24)
	50–64	0.81 (55)	0.46 (31)	0.56 (0.36, 0.87)	43.68 (13.16, 64.13)	0.36 (0.09, 0.62)
	≥65	0.84 (44)	0.37 (24)	0.44 (0.27, 0.72)	55.65 (27.77, 73.43)	0.47 (0.18, 0.76)
	All	0.57 (180)	0.25 (83)	0.45 (0.34, 0.58)	55.29 (42.23, 65.68)	0.31 (0.21, 0.41)
Non-PCV13 serotypes						
	0–4	0.12 (2)	0.50 (9)	4.37 (1.13, 28.68)	–337.29 (–2768.43, –12.7)	–0.39 (–0.75, –0.02)
	5–17	0.04 (2)	0.02 (1)	0.52 (0.02, 5.42)	48.09 (–441.95, 97.59)	0.02 (–0.05, 0.09)
	18–49	0.12 (16)	0.16 (21)	1.32 (0.69, 2.57)	–32.08 (–157.05, 30.81)	–0.04 (–0.13, 0.05)
	50–64	0.53 (36)	0.43 (29)	0.81 (0.49, 1.31)	19.5 (–31.03, 50.97)	0.1 (–0.13, 0.34)
	≥65	0.23 (12)	0.78 (50)	3.39 (1.87, 6.67)	–238.75 (–566.6, –86.85)	–0.55 (–0.8, –0.3)
	All	0.21 (68)	0.34 (110)	1.57 (1.16, 2.13)	–56.85 (–113.12, –16.28)	–0.12 (–0.2, –0.04)
PCV13-PCV10 serotypes (3, 6A, 19A)						
	0–4	0.12 (2)	0.06 (1)	0.49 (0.02, 5.07)	51.41 (–407.28, 97.74)	0.06 (–0.13, 0.25)
	5–17	0.04 (2)	0 (0)	0 (0, 1.62)	100 (–61.61, 100)	0.04 (–0.02, 0.1)
	18–49	0.01 (1)	0.05 (6)	6.04 (1.03, 114.04)	–503.82 (–11303.54, –3.15)	–0.04 (–0.08, 0)
	50–64	0.13 (9)	0.21 (14)	1.55 (0.68, 3.73)	–55.45 (–273.16, 31.81)	–0.07 (–0.21, 0.07)
	≥65	0.13 (7)	0.16 (10)	1.16 (0.45, 3.20)	–16.14 (–219.85, 55.39)	–0.02 (–0.16, 0.12)
	All	0.07 (21)	0.10 (31)	1.43 (0.83, 2.53)	–43.14 (–152.46, 17.22)	–0.03 (–0.07, 0.02)
PPSV23 unique serotypes						
	0–4	0 (0)	0.22 (4)	–	–	–0.22 (–0.44, 0)
	5–17	0.02 (1)	0.021 (1)	1.04 (0.04, 26.25)	–3.82 (–2525.4, 95.89)	0 (–0.06, 0.06)
	18–49	0.06 (8)	0.08 (11)	1.38 (0.56, 3.57)	–38.37 (–257.43, 43.99)	–0.02 (–0.09, 0.04)
	50–64	0.27 (18)	0.21 (14)	0.78 (0.38, 1.56)	22.28 (–55.78, 62.01)	0.06 (–0.1, 0.22)
	≥65	0.13 (7)	0.33 (21)	2.44 (1.09, 6.19)	–143.9 (–519.26, –8.77)	–0.19 (–0.36, –0.02)
	All	0.11 (34)	0.16 (51)	1.45 (0.95, 2.26)	–45.45 (–126.28, 5.33)	–0.05 (–0.1, 0.01)
3						
	0–4	0.06 (1)	0.06 (1)	0.97 (0.04, 24.57)	2.82 (–2357.41, 96.16)	0 (–0.16, 0.16)
	5–17	0.04 (2)	0 (0)	0 (0, 1.62)	100 (–61.61, 100)	0.04 (–0.02, 0.1)
	18–49	0 (0)	0.02 (2)	–	–	–0.02 (–0.04, 0.01)
	50–64	0.04 (3)	0.04 (3)	1.0 (0.19, 5.40)	0.07 (–439.95, 81.51)	0 (–0.07, 0.07)
	≥65	0.08 (4)	0.06 (4)	0.81 (0.19, 3.44)	18.7 (–243.84, 80.78)	0.01 (–0.08, 0.11)
	All	0.03 (10)	0.03 (10)	0.97 (0.40, 2.36)	3.04 (–136.28, 60.21)	0 (–0.03, 0.03)
6A						
	0–4	0.06 (1)	0 (0)	0 (0, 5.87)	100 (–487.09, 100)	0.06 (–0.06, 0.17)
	5–17	0 (0)	0 (0)	–	–	–
	18–49	0.01 (1)	0.01 (1)	1.01 (0.04, 25.45)	–0.64 (–2444.9, 96.02)	0 (–0.02, 0.02)
	50–64	0.07 (5)	0.09 (6)	1.20 (0.36, 4.16)	–19.91 (–316.09, 63.88)	–0.01 (–0.11, 0.08)
	≥65	0.08 (4)	0.06 (4)	0.81 (0.19, 3.44)	18.7 (–243.84, 80.78)	0.01 (–0.08, 0.11)
	All	0.03 (10)	0.03 (9)	0.87 (0.35, 2.17)	12.73 (–116.51, 65.33)	0 (–0.02, 0.03)

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Table 1 (continued)

	Age group (years)	Pre-PCV10 period Incidence rate per 100,000 person-years (N)	PCV10 period Incidence rate per 100,000 person-years (N)	PCV10 period vs. Pre-PCV10 period		
				Incidence rate ratio	Relative rate reduction (%)	Absolute rate reduction/100,000 person-years
6C	0–4	0 (0)	0.11 (2)	–	–	–0.11 (–0.27, 0.04)
	5–17	0 (0)	0 (0)	–	–	–
	18–49	0 (0)	0.03 (4)	–	–	–0.03 (–0.06, 0)
	50–64	0.02 (1)	0.04 (3)	3.0 (0.38, 60.61)	–199.79 (–5960.57, 61.62)	–0.03 (–0.09, 0.03)
	≥65	0.04 (2)	0.09 (6)	2.44 (0.56, 16.65)	–143.9 (–1564.69, 43.8)	–0.06 (–0.15, 0.04)
	All	0.01 (3)	0.05 (15)	4.85 (1.6, 20.93)	–384.82 (–1993.23, –60)	–0.04 (–0.06, –0.01)
19A	0–4	0 (0)	0 (0)	–	–	–
	5–17	0 (0)	0 (0)	–	–	–
	18–49	0 (0)	0.02 (3)	–	–	–0.02 (–0.05, 0)
	50–64	0.02 (1)	0.07 (5)	5.00 (0.81, 95.73)	–399.65 (–9472.74, 19.42)	–0.06 (–0.13, 0.01)
	≥65	0 (0)	0.06 (4)	–	–	–0.06 (–0.12, 0)
	All	0.00 (1)	0.04 (12)	11.64 (2.29, 211.99)	–1063.56 (–21099.18, –129.33)	–0.03 (–0.06, –0.01)
22F	0–4	0 (0)	0.06 (1)	–	–	–0.06 (–0.17, 0.05)
	5–17	0 (0)	0 (0)	–	–	–
	18–49	0.03 (4)	0.02 (3)	0.76 (0.15, 3.42)	24.52 (–242.4, 85.13)	0.01 (–0.03, 0.05)
	50–64	0.04 (3)	0.10 (7)	2.33 (0.65, 10.82)	–133.17 (–981.94, 35.18)	–0.06 (–0.15, 0.03)
	≥65	0.06 (3)	0.16 (10)	2.71 (0.83, 12.09)	–171 (–1108.77, 17.1)	–0.1 (–0.21, 0.02)
	All	0.03 (10)	0.06 (21)	2.04 (0.98, 4.52)	–103.62 (–351.53, 1.71)	–0.03 (–0.07, 0)

* Includes cases with missing serotype information.

3.1.4. Case fatality proportions and mortality rates

We identified 64 PM-related deaths which occurred within 30 days of the first positive culture (40 deaths in pre-PCV10 period and 24 deaths in PCV10-period). All identified deaths, except one, were in adults ≥ 18 years of age (Table 2). Compared with the pre-PCV10 baseline period, the overall mortality rate related to all PM decreased by 42% (95%CI 4%–65%) from 0.13 to 0.07 deaths per 100,000 person-years. This was primarily due to 66% (95%CI 31%–85%) reduction in mortality rate for PCV10 serotype PM (Table 2), particularly in persons 50–64 years of age (reduction by 80% (95%CI 39%–95%)). The overall CFPs during the pre-PCV10 period and PCV10 period were 16% and 12%, respectively ($p = 0.41$). The CFP in persons 50–64 years of age decreased from 25% in pre-PCV10 period to 10% in PCV10-period ($p = 0.04$).

In adults ≥ 18 years of age, the PM-related mortality rate decreased by 41% (95%CI 3%–65%) from 0.16 to 0.09 deaths per 100,000 person-years, mainly due to decrease by 65% (95%CI 29%–85%) in mortality rate for PCV10 serotype PM. The CFPs in pre-PCV10 period and PCV10 period were 19% and 14%, respectively ($p = 0.61$).

4. Discussion

Seven years of infant PCV10 program has resulted in substantial reduction in the burden of pneumococcal meningitis in Finland. The overall incidence of PCV10 serotype meningitis was reduced by 68% and, consequently, the overall PM incidence by 27%. In vaccine-eligible children, there was an 87% reduction in the incidence of PCV10 serotype cases and in 2017, no PCV10 serotype meningitis cases were seen. The overall PM-related mortality rate was reduced by 42%. The case fatality proportion decreased from 25% to 10% in persons 50–64 years. However, an important burden of disease remains in older adults because of an increase in PM caused by non-PCV10 serotypes.

Our study suggests substantial herd effect of vaccination, since incidence rates of PCV10 serotypes cases decreased not only in vaccinated children, but also in non-vaccinated population groups

including older adults ≥ 65 years of age. However, because of serotype replacement, no net impact of PCV10 on disease burden was seen in the older adult age group. In the final study year, the significant decrease in PCV10 serotype PM was offset mostly by disease caused by serotype 22F (included in PPSV23) and non-vaccine serotypes such as 6C and 23A. This suggests relatively small potential benefits of PCV13 vaccination for older adults and a potential advantage of PPSV23 in terms of covered serotypes.

Serotype replacement has been widely reported after introduction of pneumococcal vaccines. After PCV7 introduction, meningitis cases caused by non-PCV7 serotypes emerged, particularly serotypes 1, 3, 7F, 19A and 22F [25–28]. After introduction of higher valency vaccines, significant reductions in PM have been reported among children < 5 years in France, England and Wales and Israel due to decreases in the additional serotypes included in PCV13 [14,29,30]. Among U.S. children and Israeli adults, the number of PM cases remained almost unchanged despite a decrease in the proportion of PCV13 serotypes after PCV13 introduction [16,31]. The most frequent emerging non-PCV13 serotypes during PCV13 vaccination period have been 8 and 12F in England and Wales [29]; 12F, 24F, 23B and 10A in France [14]; 12F, 16F, 6C, 23A, 23B, and 24F in Israel [16]; and 22F and 35B among U.S. children [31]. In the US, serotype 19A continued to be the most common PM serotype after three years of infant PCV13 vaccination program [31]. In Brazil where PCV10 was implemented, PM in children decreased significantly after introduction. Non-PCV10 serotypes 12F, 10A, 15B and 18B were reportedly most prevalent during PCV10 period [32].

In our study, the incidence of serotype 6A PM was low and did not change after PCV10 introduction. In PCV10-period, however, we saw an increase in serotype 6C in adults ≥ 18 years of age. Emergence of this IPD serotype has been noted also in other settings, including those using PCV13 [16,33].

Regardless of age, PM incidence of serotype 3 has not changed in PCV10 period. In Brazil, increase in serotype 3 was found in patients aged over 18 years with a diagnosis other than meningitis [19]. In Israel, serotype 3 PM increased after PCV13 introduction

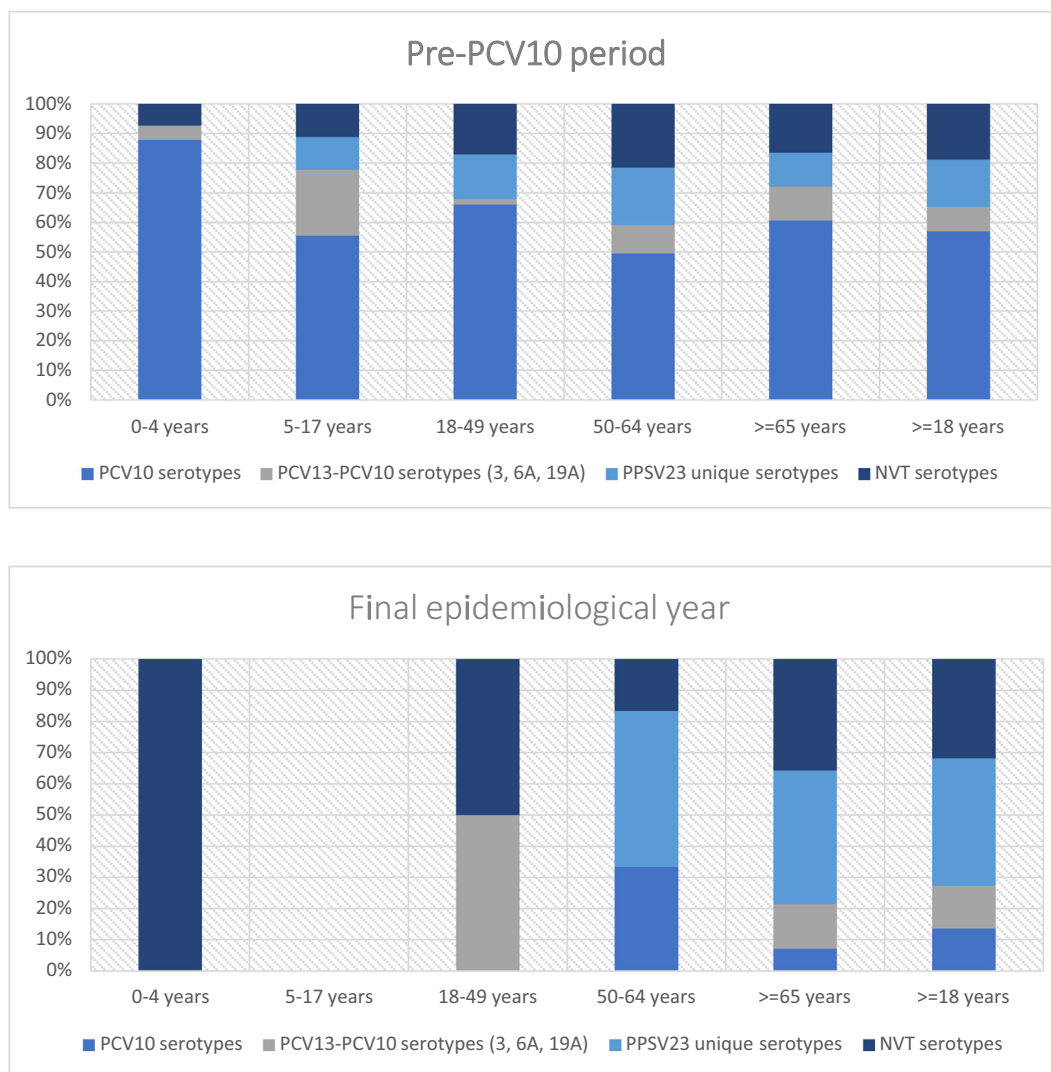


Fig. 2. Proportions of pneumococcal meningitis (PM) according to serotype in age groups in the pre-PCV10 period and in the final epidemiological year (2016–2017) of the study, Finland.

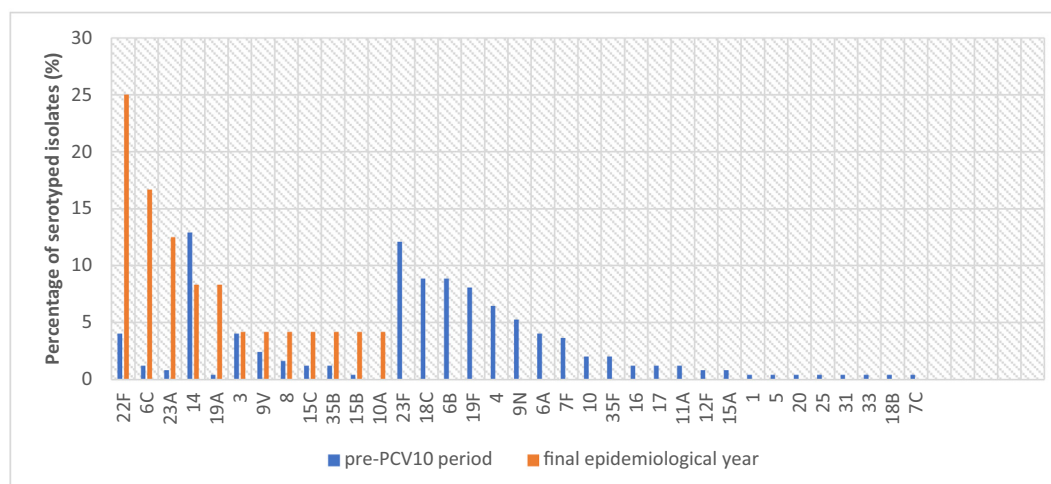


Fig. 3. Contribution (percentage) of individual *Streptococcus pneumoniae* serotypes to pneumococcal meningitis cases for all age groups before PCV10 introduction and in the final epidemiological year of the study (2016–2017), Finland.

Table 2

Mortality rates of pneumococcal meningitis (PM) and the corresponding relative and absolute rate reduction, based on the comparison of the pre-PCV10 period vs PCV10 period, Finland.

		Pre-PCV10 period		PCV10 period		Pre-PCV10 period vs PCV10 period		
	Age group (years)	Mortality/ 100,000 person-years (N)	CFP (%)	Mortality/ 100000 person-years (N)	CFP (%)	Mortality rate ratio	Relative rate reduction, %	Absolute rate reduction/ 100,000 person-years
Any culture confirmed								
	0–4	0.06 (1)	2.4	0 (0)	0.0	0 (0, 5.87)	100 (–487.09, 100)	0.06 (–0.06, 0.17)
	5–17	0 (0)	0.0	0 (0)	0.0	–	–	–
	18–49	0.05 (6)	11.3	0.04 (5)	12.5	0.84 (0.24, 2.78)	16.14 (–178.45, 75.83)	0.01 (–0.04, 0.06)
	50–64	0.34 (23)	24.7	0.09 (6)	9.8	0.26 (0.10, 0.60)	73.93 (39.92, 90.37)	0.25 (0.1, 0.41)
	>=65	0.19 (10)	16.4	0.20 (13)	17.6	1.06 (0.47, 2.48)	–5.69 (–147.59, 53.51)	–0.01 (–0.17, 0.15)
	All	0.13 (40)	15.6	0.07 (24)	12.4	0.58 (0.35, 0.96)	41.82 (4.26, 65.4)	0.05 (0, 0.1)
PCV10-serotypes								
	0–4	0.06 (1)	2.8	0 (0)	0.0	0 (0, 5.87)	100 (–487.09, 100)	0.06 (–0.06, 0.17)
	5–17	0 (0)	0.0	0 (0)	0.0	–	–	–
	18–49	0.03 (4)	11.4	0.02 (3)	23.1	0.76 (0.15, 3.42)	24.52 (–242.4, 85.13)	0.01 (–0.03, 0.05)
	50–64	0.22 (15)	32.6	0.04 (3)	17.6	0.2 (0.05, 0.61)	80.01 (39.44, 95.37)	0.18 (0.05, 0.3)
	>=65	0.12 (6)	16.2	0.05 (3)	21.4	0.41 (0.09, 1.54)	59.35 (–54.08, 91.42)	0.07 (–0.04, 0.17)
	All	0.08 (26)	16.4	0.03 (9)	17.3	0.34 (0.15, 0.69)	66.44 (31, 85.14)	0.05 (0.02, 0.09)
Non-PCV10 serotypes								
	0–4	0 (0)	0.0	0 (0)	0.0	–	–	–
	5–17	0 (0)	0.0	0 (0)	0.0	–	–	–
	18–49	0.02 (2)	11.8	0.02 (2)	7.4	1.01 (0.12, 8.39)	–0.64 (–738.79, 87.93)	0 (–0.03, 0.03)
	50–64	0.12 (8)	17.8	0.04 (3)	7.0	0.38 (0.08, 1.30)	62.53 (–29.56, 91.79)	0.07 (–0.02, 0.17)
	>=65	0.08 (4)	21.1	0.16 (10)	16.7	2.03 (0.68, 7.41)	–103.25 (–640.99, 32.01)	–0.08 (–0.2, 0.04)
	All	0.04 (14)	15.7	0.05 (15)	10.6	1.04 (0.50, 2.18)	–3.89 (–117.65, 50.1)	0 (–0.03, 0.03)
PCV13-serotypes								
	0–4	0.06 (1)	2.6	0 (0)	0.0	0 (0, 5.87)	100 (–487.09, 100)	0.06 (–0.06, 0.17)
	5–17	0 (0)	0.0	0 (0)	0.0	–	–	–
	18–49	0.03 (4)	11.1	0.02 (3)	15.8	0.76 (0.150, 3.42)	24.52 (–242.4, 85.13)	0.01 (–0.03, 0.05)
	50–64	0.25 (17)	30.9	0.07 (5)	16.1	0.29 (0.10, 0.74)	70.61 (25.7, 90.34)	0.18 (0.04, 0.31)
	>=65	0.12 (6)	13.6	0.05 (3)	12.5	0.41 (0.09, 1.54)	59.35 (–54.08, 91.42)	0.07 (–0.04, 0.17)
	All	0.09 (28)	15.6	0.03 (11)	13.3	0.38 (0.18, 0.74)	61.91 (25.62, 81.84)	0.05 (0.02, 0.09)
Non-PCV13 serotypes								
	0–4	0 (0)	0.0	0 (0)	0.0	–	–	–
	5–17	0 (0)	0.0	0 (0)	0.0	–	–	–
	18–49	0.02 (2)	12.5	0.02 (2)	9.5	1.01 (0.12, 8.39)	–0.64 (–738.79, 87.93)	0 (–0.03, 0.03)
	50–64	0.09 (6)	16.7	0.02 (1)	3.4	0.17 (0.01, 0.98)	83.35 (2.51, 99.12)	0.07 (0, 0.15)
	>=65	0.08 (4)	33.3	0.16 (10)	20.0	2.03 (0.68, 7.41)	–103.25 (–640.99, 32.01)	–0.08 (–0.2, 0.04)
	All	0.04 (12)	17.6	0.04 (13)	11.8	1.05 (0.48, 2.34)	–5.04 (–133.53, 52.35)	0 (–0.03, 0.03)
PCV13-PCV10 serotypes (3, 6A, 19A)								
	0–4	0 (0)	0.0	0 (0)	0.0	–	–	–
	5–17	0 (0)	0.0	0 (0)	–	–	–	–
	18–49	0 (0)	0.0	0 (0)	0.0	–	–	–
	50–64	0.03 (2)	22.2	0.03 (2)	14.3	1.00 (0.12, 8.33)	0.07 (–732.9, 88.01)	0 (–0.06, 0.06)
	>=65	0 (0)	0.0	0 (0)	0.0	–	–	–
	All	0.01 (2)	9.5	0.01(2)	6.5	0.97 (0.12, 8.08)	3.04 (–708.18, 88.37)	0 (–0.01, 0.01)
PPSV23 unique serotypes								
	0–4	0 (0)	–	0 (0)	0.0	–	–	–
	5–17	0 (0)	0.0	0 (0)	0.0	–	–	–
	18–49	0.02 (2)	25.0	0.02 (2)	18.2	1.01 (0.12, 8.39)	–0.64 (–738.79, 87.93)	0 (–0.03, 0.03)
	50–64	0.04 (3)	16.7	0.02 (1)	7.1	0.33 (0.02, 2.60)	66.69 (–160.17, 98.35)	0.03 (–0.03, 0.09)
	>=65	0.08 (4)	57.1	0.08 (5)	23.8	1.02 (0.27, 4.11)	–1.63 (–310.59, 73.11)	0 (–0.1, 0.1)
	All	0.03 (9)	26.5	0.02 (8)	15.7	0.86 (0.32, 2.25)	13.81 (–125.43, 67.64)	0 (–0.02, 0.03)

[16]. Serotype 3 has been a common replacing serotype in adult IPD. Study results regarding direct PCV13 effectiveness against IPD serotype 3 have been inconsistent, and some suggest poor immunogenicity and effectiveness [34–38]. Several reports on IPD suggest no indirect protection from PCV13 against serotype 3 [39,40].

In our study, no cases of serotype 19A PM were seen in children, but its incidence increased significantly in adults ≥ 18 years of age. These findings are consistent with other studies [41]. In many European countries and the US after PCV7 introduction, serotype 19A emerged as the most common replacing serotype causing meningitis [42]. Emergence of this serotype might be related to high prevalence of 19A carriage during pre-vaccination period, antimicrobial non-susceptibility and capsular switching [43]. Con-

tinuous surveillance will be essential in determining whether serotype replacement will lead to increases in serotype 19A meningitis in Finland.

PCV10 vaccination has had an impact not only on morbidity, but also on PM-associated mortality. The overall PM-associated mortality rate was reduced by 42%. In the PCV10 period, there were no deaths related to PM in children < 18 years. In adults 50–64 years of age, where the burden of disease is high, PM-associated mortality rate was reduced by 74% and case fatality by 15%. The reduction in PM related mortality was mostly due to decrease in PCV10 serotype-related fatal cases. These results are consistent with other studies conducted with either PCV13 or PCV10 in the US and Brazil [44,45]. The reduction in PM associated mortality and overall CFP might be due to lower invasive potential

of the replacing pneumococcal strains and/or changes in clinical practice, such as use of adjunctive dexamethasone therapy [46,47].

Some limitations should be considered with our data. First, the observational before-after comparison study design is susceptible to bias due to secular trends, potential changes in reporting system, clinical practices and prevalence of risk factors. The estimated magnitude and precision of herd effects of pediatric PCV programs depends on the choice of analytical methodology. For datasets where, upward trends in overall IPD were reported before vaccine introduction, substantially larger estimated herd effects might be observed in interrupted time series (ITS) analysis, than in before-after analysis. In such a situation, before-after analysis is characterized by smaller differences in observed and expected IRRs and smaller or no herd effects, since pre-vaccine trends are averaged out [48]. In Finland there have been no major changes in meningitis case ascertainment since 1995 and no trend in PM incidence was observed before PCV10 introduction [49]. Therefore, we choose not to adjust for trend in our analysis. Information of comorbidities and treatment were not available in surveillance data. Secondly, we did not have information on cause of deaths. However, most of the deaths associated with bacterial meningitis occurred early (within 14 days of admission), suggesting that they were related to the infection. Due to very small number of fatal cases, it was not possible to assess the association between particular serotype and risk of death. According to the National vaccination register, the uptake of adult PCV13 vaccinations was about 8% and that of PPSV23 about 2% during the study period. It is therefore unlikely that adult vaccinations influenced the results.

The study has several strengths. First, we used data from national, laboratory-based surveillance system that allows near complete case ascertainment and serotyping. The linking of the National Infectious Diseases Register database with the Population Information System of Finland allows conducting whole population analyses and provides accurate population denominators. In addition, Inclusion of PM cases based on ICD-10 discharge data and positive blood culture results increased the sensitivity of case definition and reduced misclassification.

In conclusion, our study contributes to the evidence-base of PCV10 impact on PM in vaccinated children and herd effects on vaccine type PM in unvaccinated age groups. Importantly, substantial reductions in both PM incidence and associated mortality rates were seen in working-age adults 50–64 years of age among whom the PM burden was high. In older adults ≥ 65 years of age, however, the burden remains unchanged because of serotype replacement. Cost-effectiveness studies of higher-valency infant and adult vaccination strategies should be considered to achieve optimal vaccination program for prevention of pneumococcal meningitis.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [The Finnish Institute for Health and Welfare has received research funding from GlaxoSmithKline Vaccines for the conduct of a nationwide effectiveness trial of the 10-valent pneumococcal conjugate vaccine, and from Pfizer, Inc. and Sanofi Pasteur, Inc. for non-pneumococcal research. Hanna Rinta-Kokko, Arto A. Palmu and Maija Toropainen are co-investigators in these studies. The other authors have no conflicts to disclose. The current study was entirely publicly funded.].

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Appendix A. Supplementary data

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