Long-term population impact of infant 10-valent pneumococcal conjugate vaccination on invasive pneumococcal disease in adults in Finland

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ABSTRACT

Background: Limited data are available on long-term indirect effects of ten-valent pneumococcal conjugate vaccine (PCV10) programmes. We evaluated changes in invasive pneumococcal disease (IPD) incidence, mortality, and serotype distribution in adults up to 9 years after infant PCV10 introduction.
Methods: Culture-confirmed IPD cases $\geq$18 years (n = 5610; 85% were pneumonia) were identified through national, population-based laboratory surveillance; data were linked with population registry to conduct nationwide follow-up study. In a time-series model, we compared serotype-specific IPD incidence and associated 30-day mortality rates before and after PCV10 by using negative binomial regression models.
Results: During pre-PCV10 period (7/2004–6/2010), overall IPD incidence in adults $\geq$18 years increased yearly by 4.8%. After adjusting for trend and seasonality, the observed PCV10 serotype IPD incidence in 7/2018–6/2019 was 90% (12/100,000 person-years) lower than the expected rate without PCV10 program. Non-PCV10 serotype incidence was 40% (4.4/100,000 person-years) higher than expected; serotypes 3, 19A, 22F, and 6C accounted for most of the rate increase. However, incidence of non-PCV10 IPD levelled off by end of follow-up. The observed-expected incidence rate-ratio (IRR) was 0·7 (95 %CI 0·5–0.8) for all IPD and 0·7 (95 %CI 0·3–1·3) for IPD-associated 30-day mortality. Case-fatality proportion decreased from 11·9% to 10.0% (p < 0.01). In persons $\geq$65 years, the IRR was 0·7 (95 %CI 0·5–0.95).
Conclusions: Significant indirect effects were seen for vaccine-serotype IPD and for overall IPD in all adult age groups. For non-vaccine IPD, the incidence stabilized 5 years after infant PVC10 program introduction, resulting in a steady state in which non-vaccine IPD accounted for nearly 90% of overall IPD. Substantial pneumococcal disease burden remains in older adults.

1. Introduction

Invasive pneumococcal disease (IPD) remains a significant public health problem, particularly among older adults, who experience considerable mortality from pneumococcal diseases. In adults, the most common clinical manifestation of IPD is bacteremic pneumococcal pneumonia. As the disease burden and population-level effects of infant pneumococcal conjugate vaccine (PCV) programs, such as indirect effects and changes in serotype distribution can generally not be evaluated in randomized con-trolled trials (RCTs), long-term population-based observational studies are needed to assess the overall public health impact of national vaccination programs (NVPs).

The bulk of currently available data on the population-level impact and indirect effects of PCVs come from 7-valent (PCV7) [1,2] and 13-valent (PCV13) program experience [3–6]. In Finland, a cluster-RCT demonstrated the effectiveness of 10-valent pneumococcal conjugate vaccine (PCV10) in infants [7] and, after its introduction in the NVP, significant decreases in IPD incidence were documented in both vaccine-eligible and unvaccinated, older children [8,9]. Few data, however, are available on the long-term indirect effects in adults from settings in which PCV10 has been used exclusively in NVPs, [10–13] particularly in populations without previous PCV use. We conducted a nationwide,

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population-based, observational follow-up study to assess long-term changes in the burden of laboratory-confirmed IPD and associated 30-day mortality in adults 9 years after infant PCV10 introduction.

2. Methods

2.1. Vaccination program

Infant PCV10 vaccination began in September 2010 as the first PCV in the Finnish NVP. In a 2 + 1 schedule, vaccinations are given at 3, 5, and 12 months of age. Although there was no initial catch-up, uptake increased rapidly and coverage of ≥1 doses in the 2012 birth cohort was 94%. Use of 23-valent pneumococcal polysaccharide vaccine (PPSV23) and PCV13 is recommended for adults with risk factors, but no national adult vaccination program is currently implemented. Based on National vaccine registry data, the cumulative adult coverage for PPSV23 and PCV13 in 2018 was 3% and 9%, respectively [14].

2.2. Study population, surveillance, and laboratory methods

The Population Information System (PIS) includes data on all ~5·5 million permanent residents in Finland. A unique personal identity code (PIC) enables linking IPD surveillance data with various national health databases. Diagnosis and treatment of IPD takes place in public acute care hospitals. All clinical microbiology laboratories (n = 22) report isolations of *Streptococcus pneumoniae* from blood or cerebrospinal fluid (CSF) to the National Infectious Disease Register (NIDR), a population-based, electronic laboratory surveillance system maintained by the Finnish Institute for Health and Welfare (THL) since 1995 (routine notifications have included the PIC since 2004). Multiple notifications concerning the same individual within three months from the first notification are combined into a single case [15].

The study target population was defined as the Finnish adult population ≥18 years of age from July 2011 to June 2019 (PCV10 period). The reference population was the adult population from July 2004 to June 2010 (pre-PCV10 baseline). We compared rates between these populations; person-years (PYs) of follow-up (35,190·633 and 25,162·151, respectively) were obtained from PIS. The epidemiologic year 2010–2011 was considered a transition period and excluded.

Clinical microbiology laboratories have a legal requirement to submit pneumococcal isolates from reported cases to THL reference laboratory. After species verification, pneumococcal isolates were serotyped by latex agglutination and/or counterimmunoelectrophoresis supplemented with Quellung reaction until 2009. Since 2010, isolates have been serotyped by multiplex PCR supplemented with Quellung reaction, if needed, [16] and identification of serotypes 6C and 6D is done routinely. All serotype 6A isolates from 2004 to 2009 were re-tested to distinguish serotype 6C cases.

2.3. Case definitions

A case of IPD was defined as isolation of *S. pneumoniae* from blood or CSF with culture dates from July 1, 2004 to June 30, 2019 and reported to the NIDR. Cases were categorized into PCV10-serotypes (1, 4, 5, 6B, 7F, 9 V, 14, 18C, 19F, 23F) and non-PCV10 types. Additional analysis groups included PCV13 serotypes (PCV10 + 3, 6A, 19A) and the 11 serotypes unique to PPSV23. The clinical syndrome (bacteremic pneumonia, meningitis, bacteremia, other) was defined based on ICD-10-coded diagnoses in the national hospital discharge register. A death was considered IPD-associated if it occurred within 30 days of the first positive culture;

dates of death were verified from the PIS but cause of death data were not available.

2.4. Statistical analysis

We calculated overall, age-, and serotype group-specific incidence of IPD, the associated 30-day mortality rates, and case-fatality proportions (CFP). To evaluate timing of death in relation to the IPD episode, the observed daily hazard of death during 90 days after the first positive IPD culture date was compared with the expected daily hazard of death in an age- and sex-adjusted Finnish general population [17].

To adjust for pre-PCV10 trend in IPD incidence, seasonality, and changes in the population size, we conducted an interrupted time-series analysis. Separate models were fitted for IPD and IPD-associated mortality data by age and vaccine-serotype-group. Monthly incidence and mortality rates were modelled by using a negative binomial regression model: $\log E(Y_t) = \beta_0 + \beta_1 T_t + \beta_2 X_t + \beta_3 X_t T_t + \beta_4 \sin[2\pi t/12] + \beta_5 \cos[2\pi t/12] + \log(P_{opt}/100000)$, in which β_0 is baseline rate, T is time since study beginning until month t and $X_t T_t$ is an interaction term. β_1 and β_3 represent the pre- and post-vaccine trends, respectively. β_2 represents the estimated vaccine effect; X is 0 during pre-PCV10 period and 1 during PCV10 period. The sine and cosine terms adjust for seasonality. Monthly population size was included as offset in the model. The expected incidence and mortality rates during the PCV10 period, had the vaccine not been introduced, were predicted by holding the model parameters denoting vaccine effect and trend after PCV10 introduction at zero. We calculated ratios of observed and expected rates (Incidence Rate Ratio, IRR or Mortality Rate Ratio, MRR) and report them in the last epidemiological year of the study period (2018–2019). As a control outcome, we conducted a time-series analysis for the incidence of non-pneumococcal, laboratory-confirmed bloodstream infections reported to the NIDR from 7/2004 to 6/2018 [17] in the same age groups as the IPD analysis.

Statistical inferences of the time-series analysis were performed within the Bayesian framework. Uninformative prior distributions ($\beta \sim \text{Normal}(0, 10^6)$) were used for the predictor parameters. Separately for the observed and expected rates, we ran four parallel chains for 10,000 iterations with the first 4000 discarded as burn-in. To assess convergence of the algorithm, we used the Gelman and Rubin diagnostic [18]. All analyses were carried out with R (version 3.6.0) and the rstan library. Results are presented as point estimates (posterior mean) and 95% posterior probability (credible) intervals (CI).

2.5. True statement

Authorization for research use of surveillance data was granted by THL, the regulatory agency with jurisdiction over national health registry data (THL/1090/6.02.00/2013). THL Institutional Review Board approved the study.

3. Results

From July 1, 2004 to June 30, 2019, a total of 9833 laboratory-confirmed IPD cases in adults ≥18 years were reported to national surveillance (median age, 64 years; interquartile range 51–75 years); 98% of bacterial isolates were available for serotyping. The proportions of cases associated with specific clinical syndromes were: bacteremic pneumonia (85%), meningitis (4.5%), bacteremia or other (11.5%).

3.1. IPD incidence during pre-PCV10 and PCV10 periods

The overall average annualized IPD incidence rates per 100,000 PYs during the pre-PCV10 period (2004–2010) and the PCV10 period (2011–2019) are shown in Table 1 and Supplementary Fig. 1. During the pre-PCV10 period, the overall IPD incidence in persons ≥18 years increased gradually from 14·3 to 17·7/100,000 PYs (4.8% per year, p for trend <0.01, Fig. 1). In the two final epidemiological years (2017–2019), the overall IPD rate was 16·4/100,000 PYs. In general, the rates increased in the pre-PCV10 period across all age groups. In older age groups, rates continued to increase during the PCV period, but returned to approximately the level of PCV10 introduction by end of follow-up. The age specific IPD rates during pre-PCV10 period ranged from 7·6 to 9·5/100,000 PYs in persons 18–49 years, and from 17·6 to 20·7 in persons 50–64 years. By the end of follow-up during PCV10 period, incidence in these age groups was 6·3 and 17·5/100,000 PYs, respectively. In persons ≥65 years, the IPD incidence increased from 27·9 to 34·0/100,000 PYs during pre-PCV10 period; by the end of follow-up during PCV10 period, the rate was 33·8/100,000 PYs (Table 1, Supplementary Table 2).

3.2. Time-series model

We adjusted for pre-PCV10 trend, seasonality, and age in a time-series model (Fig. 1). The observed overall IPD incidence in persons ≥18 years in 7/2018–6/2019 was 33% lower than the expected rate without the PCV10 program (17·7 vs. 26.4/100,000 PYs; IRR 0·7; 95 %CI 0·5-0.8) (Table 2). In persons ≥65 years, the

observed overall IPD incidence was 31% lower than the expected rate (36.0 vs. 53.2/100,000 PYs; IRR 0·7; 95 %CI 0·5-0.95).

In adults ≥18 years, the observed incidence of PCV10 serotype IPD was 86% lower than the expected rate (IRR 0.1; 95% CI 0.1–0.2); consistent reductions in PCV10 serotypes were seen in all adult age-groups (Table 2, Fig. 2). The observed non-PCV10 serotype incidence, however, was higher than the expected rate (16.5 vs. 12.2/100,000 PYs; IRR 1·4; 95 %CI 0.95–1.9). In all age-groups, the credible intervals included one (Table 2, Fig. 3). For non-pneumococcal bloodstream infections, which were evaluated as a control outcome, the pre-PCV10 period trends continued during the PCV10-period; the observed incidence rates were similar to the expected incidence in all age groups (Supplementary Fig. 4).

3.3. Trends in non-PCV10 serotypes

Table 1, Supplementary Table 1, Supplementary Figure 1 and Fig. 4 show the absolute serotype-specific incidence rates before and after PCV10. During the pre-PCV10 period, non-PCV10 incidence had increased slightly from 1.7 to 2.1/100,000 PYs; serotype 3 and 22F incidence had also increased, whereas 19A and 6C incidence was stable. During the PCV10 period, the largest rate increases were seen in serotypes 19A, 3, 22F, and 6C in all adult age groups. Serotype 19A increased from 1.0 to 3.7 cases/100,000 PYs and serotype 3 from 1·6 to 3·1 cases/100,000 PYs (Fig. 4). By the end of the follow-up period, incidence of the three additional serotypes in PCV13 (19A, 3, and 6A) was 7.0/100.000 PY and that of non-PCV13 serotypes 8.8/100.000 PYs. Incidence of serotype 6C increased in all age groups, especially in age group ≥65 years (from 0.4 to 3.9/100.000 PY). Incidence of serotype 6A, however,

Table 1
Number of cases, incidence rates, and serotypes of invasive pneumococcal disease cases in adults ≥18 years of age by two epidemiological years, before and after infant PCV10 introduction, Finland July 2004–June 2019.

	Incidence rate/100 000 person-years (Number of cases*)							
	Pre-PCV10 period			Transition period	PCV10 period			
	1 July 2004 to June 2006	1 July 2006 to June 2008	1 July 2008 to June 2010	1 July 2010 to June 2011	1 July 2011 to June 2013	1 July 2013 to June 2015	1 July 2015 to June 2017	1 July 2017 to June 2019
Age group >=18 years								
Any culture confirmed IPD	14.31 (1185)	16.43 (1377)	17.72 (1506)	16.62 (713)	16.15 (1400)	15.51 (1360)	17.43 (1542)	16.43 (1463)
PCV10-serotypes	9.03 (748)	10.24 (858)	10.46 (889)	9.55 (410)	7.53 (653)	4.45 (390)	2.54 (225)	1.79 (159)
Non-PCV10 serotypes (including related)	4.66 (386)	5.81 (487)	6.51 (553)	6.78 (291)	8.46 (733)	10.92 (958)	14.8 (1309)	14.36 (1279)
Undefined	0.62 (51)	0.38 (32)	0.75 (64)	0.28 (12)	0.16 (14)	0.14 (12)	0.09 (8)	0.28 (25)
Age group 18–49 years								
Any culture confirmed IPD	7.56 (334)	8.33 (365)	9.5 (416)	8.45 (185)	6.87 (301)	6.38 (279)	6.72 (292)	6.31 (273)
PCV10-serotypes	5.29 (234)	5.75 (252)	6.16 (270)	5.53 (121)	3.95 (173)	2.33 (102)	1.24 (54)	0.74 (32)
Non-PCV10 serotypes (including related)	2.04 (90)	2.31 (101)	2.97 (130)	2.79 (61)	2.88 (126)	3.98 (174)	5.47 (238)	5.41 (234)
Undefined	0.23 (10)	0.27 (12)	0.37 (16)	0.14 (3)	0.05 (2)	0.07 (3)	0 (0)	0.16 (7)
Age group 50–64 years								
Any culture confirmed IPD	17.57 (385)	17.95 (405)	20.65 (478)	18.09 (210)	19.95 (457)	15.19 (342)	18.39 (409)	17.48 (384)
PCV10-serotypes	11.09 (243)	10.81 (244)	11.66 (270)	9.74 (113)	9.26 (212)	4.57 (103)	2.92 (65)	2.28 (50)
Non-PCV10 serotypes (including related)	5.61 (123)	6.78 (153)	8.03 (186)	8.1 (94)	10.48 (240)	10.48 (236)	15.33 (341)	14.84 (326)
Undefined	0.87 (19)	0.35 (8)	0.95 (22)	0.26 (3)	0.22 (5)	0.13 (3)	0.13 (3)	0.36 (8)
Age group >=65 years								
Any culture confirmed IPD	27.87 (466)	34.81 (607)	33.95 (612)	33.79 (318)	32.13 (642)	34.41 (739)	37 (841)	33.81 (806)
PCV10-serotypes	16.21 (271)	20.76 (362)	19.36 (349)	18.7 (176)	13.41 (268)	8.61 (185)	4.66 (106)	3.23 (77)
Non-PCV10 serotypes (including related)	10.35 (173)	13.36 (233)	13.15 (237)	14.45 (136)	18.37 (367)	25.51 (548)	32.12 (730)	30.16 (719)
Undefined	1.32 (22)	0.69 (12)	1.44 (26)	0.64 (6)	0.35 (7)	0.28 (6)	0.22 (5)	0.42 (10)

Pre-PCV10 baseline period: July 1, 2004–June 30, 2010. PCV10 period, July 1, 2011–June 30, 2019. Serotype information missing (no isolate available) for 2% of cases.
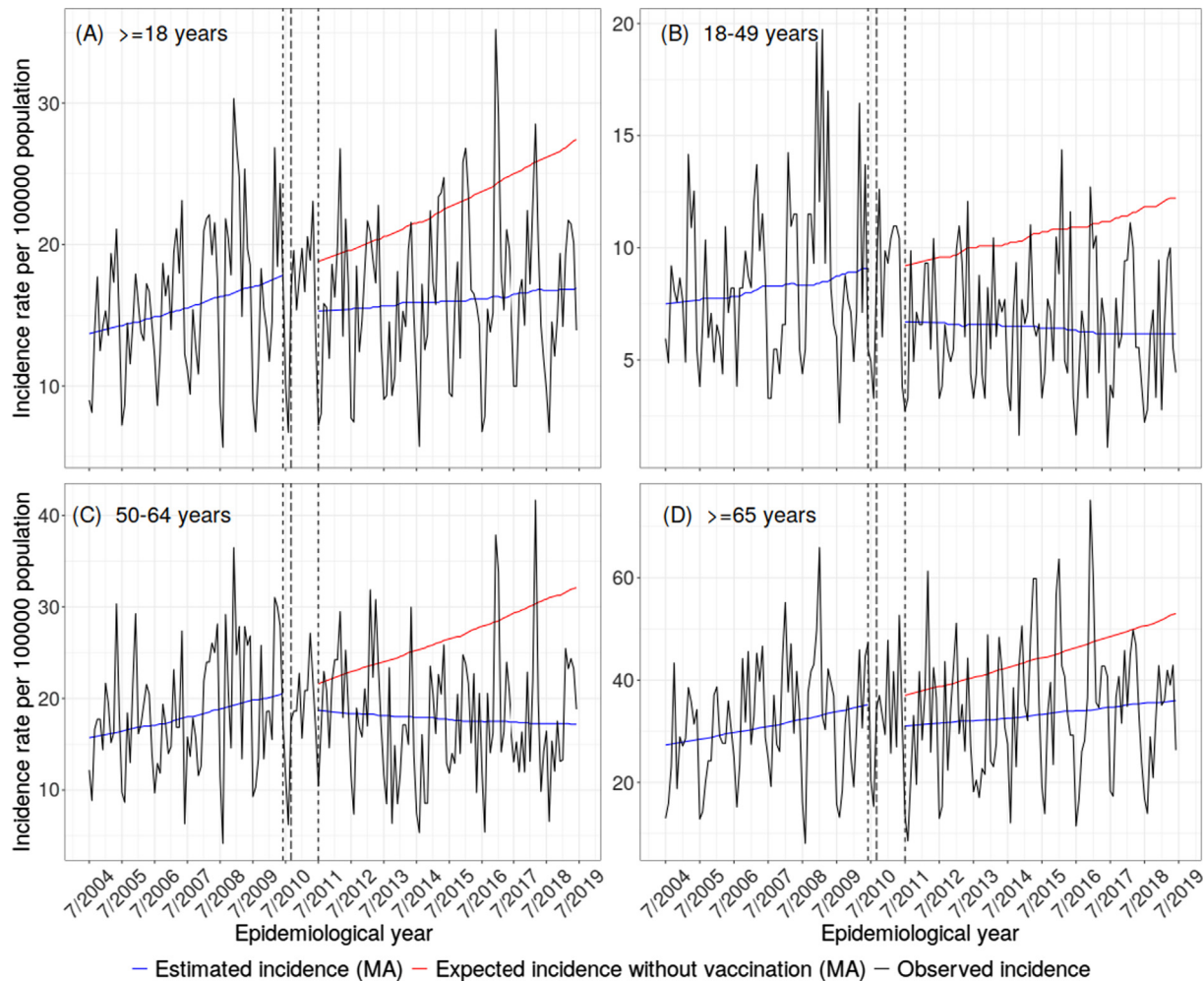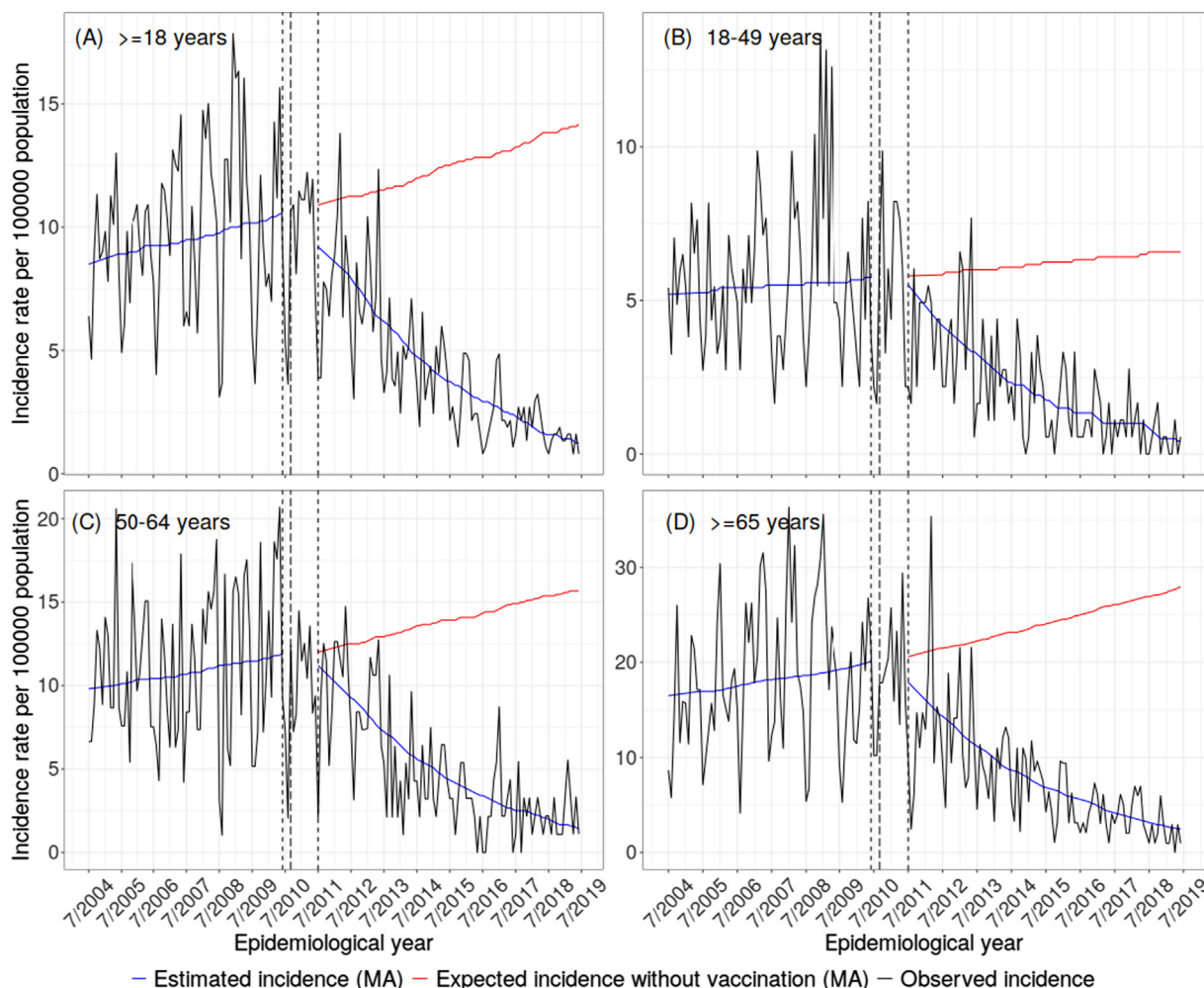
Fig. 1. Observed and expected incidence of ***all invasive pneumococcal disease*** in adults (a) >=18 years of age, (b) 18–49 years of age, (c) 50–64 years of age, and (d) >=65 years of age, interrupted time-series analysis. Negative binomial regression model adjusted for pre-PCV10 trend in IPD incidence and seasonality. Seasonal variation was smoothened by applying twelve-month moving average filters to monthly observed and expected rates. MA = moving average.

Table 2
Observed and expected incidence rates,rate ratios and rate reductions for invasive pneumococcal disease in adults ≥ 18 years of age by vaccine serotype-group, Finland July 2004 – June 2019.

	Epidemiological year 2018–2019			
	Observed incidence rate/ 100 000 person-years	Expected incidence rate/ 100 000 person-years	Relative rate ratio (95% CI)	Absolute rate reduction (95% CI)
Age group >=18 years				
Anu culture confirmed IPD	17.66	26.44	0.7 (0.5–0.8)	8.7 (3.7–15.8)
PCV10 serotypes	1.97	13.97	0.1 (0.1–0.2)	12 (7.4–18.1)
Non-PCV10 serotypes	16.52	12.15	1.4 (0.95–1.9)	−4.4 (−10.1–0.6)
Age group 18–49 years				
Anu culture confirmed IPD	6.65	12.01	0.6 (0.4–0.9)	5.3 (1.2–11.3)
PCV10 serotypes	0.94	6.82	0.1 (0.08–0.2)	6 (3–10.3)
Non-PCV10 serotypes	6.17	5.02	1.4 (0.6–2.8)	−1.2 (−4.8–3.3)
Age group 50–64 years				
Anu culture confirmed IPD	17.33	31.11	0.6 (0.4–0.8)	13.8 (3.8–27.7)
PCV10 serotypes	2.04	15.89	0.1 (0.08–0.2)	13.9 (7.0–24.2)
Non-PCV10 serotypes	16.14	16.23	1.1 (0.6–1.9)	0.05 (−8.8–11.4)
Age group >=65 years				
Anu culture confirmed IPD	35.96	53.21	0.7 (0.5–0.95)	17.2 (2–38.1)
PCV10 serotypes	3.83	27.41	0.2 (0.09–0.2)	24 (12–40.4)
Non-PCV10 serotypes	35.51	22.61	1.7 (0.9–2.7)	−12.9 (−28.1–2.4)

Interrupted time-series analysis: negative binomial regression models adjusted for pre-PCV10 trend in IPD incidence and seasonality.

Fig. 2. Observed and expected incidence of **PCV10-type invasive pneumococcal disease** in adults (a) >=18 years of age, (b) 18–49 years of age, (c) 50–64 years of age, and (d) >=65 years of age, interrupted time-series analysis. Negative binomial regression model adjusted for pre-PCV10 trend in IPD incidence and seasonality. Seasonal variation was smoothened by applying twelve-month moving average filters to monthly observed and expected rates. MA = moving average.

decreased towards the end of follow-up (Supplementary Table 1). Incidence of serotype 22F also increased in all age groups (Supplementary Table 1).

Persons ≥65 years had the greatest increases in non-PCV10 types. By 2017–2019, non-PCV10 types accounted for about 90% of IPD cases in this age group. Most common non-PCV10 serotypes were 19A (23·6%), 3 (15.6%), 6C (12.9%) and 22F (10·0%). Serotypes included in PCV13 and PPSV23 accounted for 47% and 67% of IPD cases, respectively. Non-PCV13 types, however, accounted for 53%, and serotypes not contained in any current pneumococcal vaccine for 32% of IPD cases in older adults. Serotypes included in the recently licensed PCV15 and PCV20 accounted for 58% and 66% of IPD cases during 2017–2019, respectively.

3.4. IPD-associated mortality

We identified 1042 IPD-associated deaths within 30 days of the first positive culture. Of the deaths in pre-PCV10 and PCV10 periods, 46%, and 38% occurred during days 0–2; 67% and 63% occurred during the first 7 days, respectively. The hazard of death was greatest on day one and returned to the expected hazard of death in the population in about 40 days (Supplementary Fig. 2). The overall CFP during pre-PCV10 period was 11·9% compared with 10.0% during PCV10 period (p < 0.01). According to the time-series model, the observed 30-day mortality rate associated with PCV10 sero-

type IPD decreased by 87% compared with the expected rate (0.12 vs. 1.21/100 000 PYs; MRR 0.1, 95% CI 0.04–0.3). However, as non-PCV10 incidence and, consequently, associated mortality rate increased, the overall IPD-associated MRR was 0.7 (95 %CI 0·3–1·3, Table 3).

The proportion of all IPD-associated deaths that occurred in patients ≥65 years increased from 58% to 71% (p < 0.01) from pre-PCV10 to PCV10 period; the CFP, however, decreased significantly from 16·7% to 13·7% (p < 0.01). The observed mortality rate for PCV10 serotype IPD decreased significantly by 94% compared with the expected rate. However, as the rate associated with non-PCV10 serotypes increased, the overall MRR in older adults was 0·5 (95 %CI 0·2–1·1, Table 3).

4. Discussion

Analysis of long-term national surveillance data in a setting of high infant PCV10 uptake showed that nine years after introduction, the indirect effects had significantly reduced PCV10-type invasive pneumococcal disease across all adult age groups. In addition, the proportion of fatal IPD cases declined, particularly in older adults. Indirect vaccine effects also seem to have reversed the secular pre-PCV10 increase in IPD rates in adult age-groups and overall IPD incidence appears to have reached a steady state. After adjusting for the pre-vaccine trend, the point estimate for
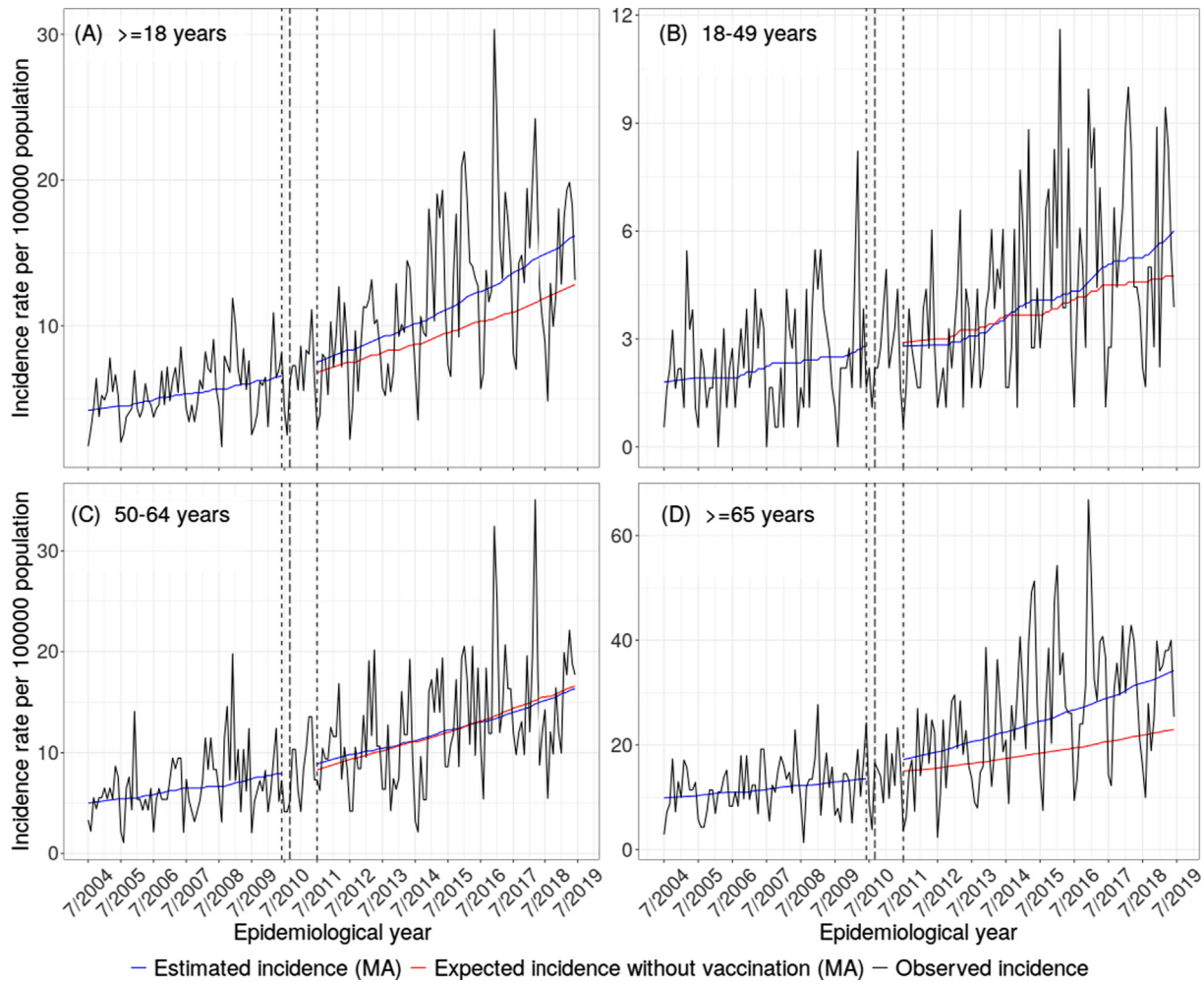
Fig. 3. Observed and expected incidence of ***non-PCV10-type invasive pneumococcal disease*** in adults (a) >=18 years of age, (b) 18–49 years of age, (c) 50–64 years of age, and (d) >=65 years of age, interrupted time-series analysis. Negative binomial regression model adjusted for pre-PCV10 trend in IPD incidence and seasonality. Seasonal variation was smoothened by applying twelve-month moving average filters to monthly observed and expected rates. MA = moving average.

reduction in overall IPD incidence in all adults was 33%. Replacement by non-PCV10 serotypes, particularly 3, 19A, 22F, and 6C was evident in all age groups. In older adults, the incidence of non-PCV10 serotypes increased and a considerable burden of pneumococcal pneumonia and bacteremia remains.

We estimated an 87% reduction in the 30-day mortality rate associated with PCV10 serotypes; in persons ≥65 years the reduction was 97%. For all IPD, the point estimate for mortality rate reduction was 30%, but the credible interval included one. The case-fatality proportion decreased, particularly in persons ≥65 years, possibly because of lower invasiveness associated with some replacement serotypes as compared with PCV10 serotypes [19,20]. Improved recognition and treatment of sepsis during the study period may also have contributed to lower case-fatality. Nevertheless, at the end of study period three quarters of all IPD-associated deaths occurred in older adults.

The most common replacement serotypes were 3, 19A, 22F, and 6C, although the absolute rate increases varied by age-group. Serotypes 3 and 19A together accounted for about half of the absolute non-vaccine type rate increase (5·4/100,000 PYs) whereas other non-PCV10 types contributed <2/100,000 PYs each. Serotypes 3 and 19A are included in PCV13 and rapid declines in serotype 19A nasopharyngeal colonization and IPD were documented shortly after introduction of infant PCV13 programs [3–5,21]. Data on PCV13 effectiveness against serotype 3 disease, however, are

inconsistent [22]. Most studies have not found reductions in serotype 3 nasopharyngeal colonization [23], or a population level impact on IPD after PCV13 introduction [4,21]. Recently, increases in serotype 3 and 19A have been reported in adults from several European settings where infant PCV13 has been used [3,6,24]. In addition, increases in a broad range of non-PCV13 serotypes have been reported after transition from PCV7 to PCV13 infant programs [3,6]. In our data, serotype 6C incidence increased across all adult age groups, but serotype 6A incidence remained constant, or decreased in younger age groups. Indirect protection from PCV13 against serotype 6A in unvaccinated adults has been reported in some settings [12,21], but not in others [3,4]. In Sweden, decreases in serotype 6A were seen in counties using PCV10 [12].

A large RCT in the Netherlands showed that PCV13 was efficacious in preventing vaccine-type IPD and non-bacteremic pneumococcal pneumonia in persons ≥65 years [25]. However, there was little impact on overall community-acquired pneumonia and no effect on mortality. The potential population impact of adult PCV13 vaccination, however, needs to be estimated by using setting-specific incidence data, the proportion of PCV13 types causing pneumococcal diseases, and the extent of non-PCV13 type replacement disease [24]. Our data in which 85% of cases were bacteremic pneumococcal pneumonia, show that by end of the study period, PCV13 serotype disease accounted for about half (36% without serotype 3) of the absolute incidence rate in persons
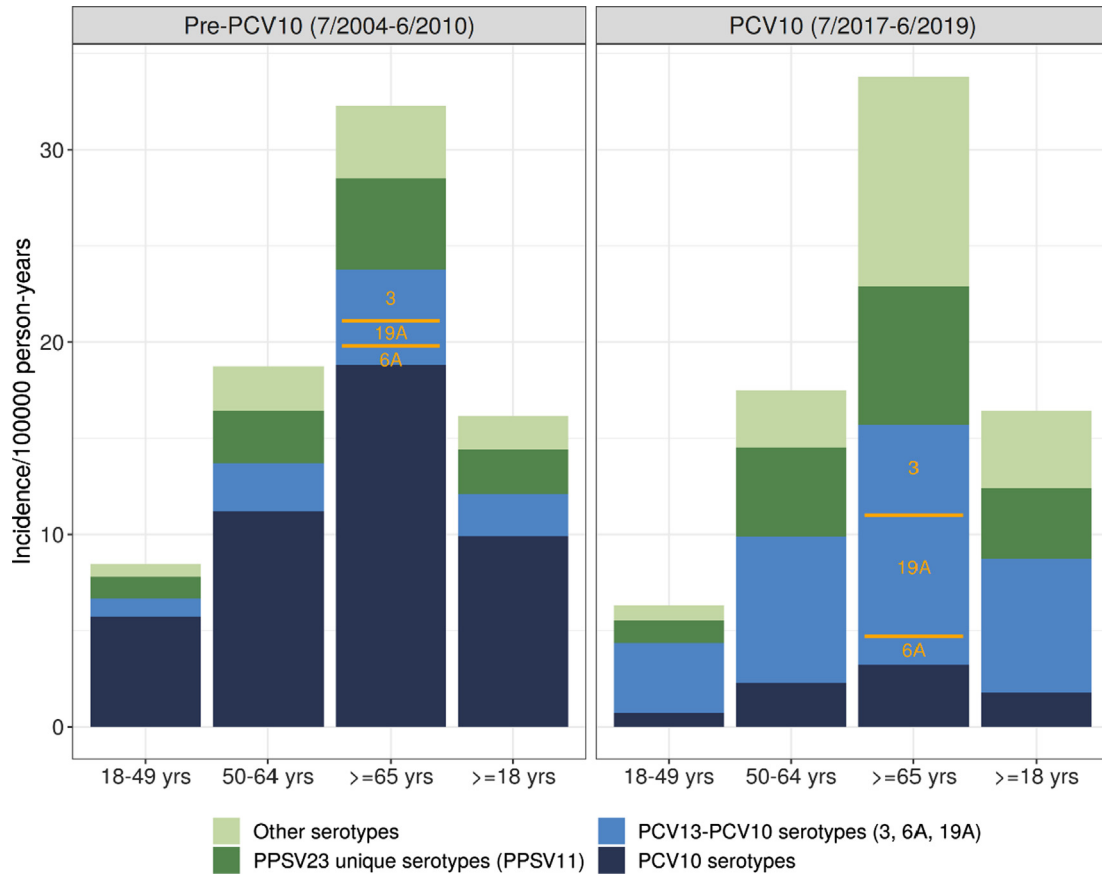
Fig. 4. Changes in absolute incidence rates of invasive pneumococcal disease in adults ≥18 years of age by pneumococcal vaccine serotype-group before and after infant PCV10 introduction. Pre-PCV10 period: July 1, 2004–June 30, 2010. PCV10-period period (last two years): July 1, 2017–June 30, 2019.

Table 3
Observed and expected 30-day mortality rates, rate ratios and rate reductions associated with invasive pneumococcal disease in adults ≥ 18 years of age by vaccine serotype-group, Finland July 2004–June 2019.

	Epidemiological year 2018–2019			
	Observed mortality rate/	Expected mortality rate/	Relative rate ratio (95% CI)	Absolute rate reduction (95% CI)
	100 000 person-years	100 000 person-years		
Age group >=18 years				
Anu culture confirmed IPD	1.53	2.4	0.7 (0.3–1.3)	0.9 (−0.4–2.8)
PCV10 serotypes	0.12	1.21	0.1 (0.04–0.3)	1.1 (0.3–2.5)
Non-PCV10 serotypes	1.44	1.21	1.5 (0.5–3.5)	−0.2 (−1.3–1.5)
Age group 18–49 years				
Anu culture confirmed IPD	0.2	0.17	2.8 (0.2–12.3)	−0.02 (−0.3–0.5)
PCV10 serotypes	0.01	0.16	0.5 (0.01–2.8)	0.2 (−0.02–0.8)
Non-PCV10 serotypes	0.16	0.04	36.7 (0.5–231.8)	−0.1 (−0.4–0.1)
Age group 50–64 years				
Anu culture confirmed IPD	1.15	2.41	0.7 (0.2–1.9)	1.3 (−0.6–5.4)
PCV10 serotypes	–	–	–	–
Non-PCV10 serotypes	0.99	3.34	0.7 (0.07–2.5)	2.4 (−0.7–13.6)
Age group >=65 years				
Anu culture confirmed IPD	4.21	9.09	0.5 (0.2–1.1)	4.8 (-0.6–14.4)
PCV10 serotypes	0.29	6.96	0.06 (0.01–0.2)	6.7 (1.5–19.5)
Non-PCV10 serotypes	4.11	3.52	1.7 (0.4–4.9)	−0.6 (-4.3–5.9)

Interrupted time-series analysis: negative binomial regression models adjusted for pre-PCV10 trend in IPD incidence and seasonality.

≥65 years, suggesting that vaccinating individuals who are at increased risk for pneumococcal disease would be reasonable based on clinical decision-making. As a population strategy, however, vaccinating older adults with PCV13 has not been found cost-effective in the context of continuing reduction of vaccine-serotype circulation due to childhood vaccination program [26].

In addition, non-PCV13 serotypes already accounted for a larger fraction of the absolute IPD incidence than PCV13 serotypes. The utility of PPSV23 might increase as disease caused by non-PCV serotypes increases. Despite its broader theoretical coverage of disease-causing serotypes, PPSV23 has no demonstrated population level impact on pneumonia in older adults and its effective-

ness against IPD in this population is controversial [27]. Furthermore, by the end of study period, serotypes not included in any current pneumococcal vaccine already accounted for a quarter of the absolute IPD rate, highlighting the need for new vaccines for older adults.

Some limitations should be considered when interpreting the findings: First, observational follow-up studies are susceptible to bias, such as secular trends, potential changes in clinical practice, and the prevalence of risk factors for pneumococcal disease. Controlling for the increasing pre-PCV10 trend in IPD incidence in a quasi-experimental time-series analysissuggested a relative decline of 31% in older adults had the pre-vaccine trend continued (Supplementary Fig. 3). However, the IPD rate initially continued to increase during the PCV10 period before it stabilized at the end of study period. In settings where the pre-vaccine IPD incidence is increasing, time-series analysis may be more appropriate analytical methodology than before-after comparison, which assumes constant incidence. However, the time-series method involves the assumption of continuation of the pre-vaccine trend which cannot always be verified. In our data, the continuing trend in the interrupted time-series analysis of control outcomes from 2004 to 2018 supported this assumption [17] (Supplementary Fig. 4). To test the robustness of our analytic approach, we conducted a supplementary analysis in which the follow-up time was three years from PCV10 implementation. The results were consistent with the main analysis, both in the magnitude of the relative rate ratios and the statistical significance level, suggesting that our model and assumptions were robust (Supplementary Table 2). As expected, the absolute rate reductions were smaller than in the main analysis, as the differences in the expected and observed rates increased with time. In addition, adjusting for overall trend may not be sufficient to control for cyclical variation in individual serotypes [28]. Comorbidities are associated with higher risk of pneumococcal disease, mortality, and possibly increased susceptibility to replacement serotypes. However, information on comorbidities and possible immunosuppression was not available in our surveillance database. The national surveillance system has been in place since 1995 with no detected changes in surveillance sensitivity during the study period [29] Although we did not have information on the specific cause of death, most deaths occurred early suggesting that they were associated with IPD. Finally, adult PCV13 or PPSV23 vaccination is unlikely to have affected the findings as cumulative uptake of both vaccines was low during the study period [14].

Few long-term data on indirect population-level impact in unvaccinated adult groups are available from countries using PCV10 in national infant vaccination programs [8–11,30]. Most previous studies have evaluated the incremental impact of substituting PCV7 with PCV10 in the immunization program. Our study, however, contributes data for better understanding the absolute population level impact of a PCV10 program, demonstrating the indirect effects (i.e., fast and consistent decrease in vaccine-type disease and gradual emergence of non-vaccine type replacement) in a PCV naive population. The timing and magnitude of indirect effects was comparable to those previously reported for PCV7 [1,2] and PCV13 from settings with robust, population-based laboratory surveillance systems and high vaccine uptake [3–6,21]. However, the serotype distributions resulting from PCV use were quite different.

Because of the unprecedented impact the public health measures implemented to contain the Covid-19 pandemic during 2020 had on the incidence of other respiratory infections, including IPD, our study provides, by chance, the longest possible follow-up duration to evaluate routine PCV10 program's population effects. Despite the major indirect protection on vaccine type IPD, associated mortality, and decline in overall adult IPD rates after nine years of infant PCV10 program, substantial burden of pneumococcal disease remains in older adults, primarily because of replacement by non-vaccine serotypes. As adult vaccination strategies to prevent pneumococcal disease need to take into consideration the differences in population-level effects of infant PCV programmes, our data have implications for public health decision-making to optimize these strategies. Given that in our study, the clinical syndrome was bacteremic pneumococcal pneumonia in 85% of IPD patients, our results are also relevant to prevention of community-acquired pneumonia, for which *Streptococcus pneumoniae* continues to be a leading cause. Ongoing, laboratory-based surveillance will be critical in monitoring future trends in serotype replacement disease among adults.

Author contributions

Study concept and design: JPN, AAP. Acquisition of data: HR-K, MT, LS. Analysis and interpretation of data: JPN, HR-K, MT, HN, AAP. Drafting of the manuscript: JPN. Critical revision of the manuscript for important intellectual content: all authors. Obtained funding: JPN. Final approval: all authors. All authors attest they meet the ICMJE criteria for authorship.

Declaration of Competing Interest

All authors are employees of the Finnish National Institute for Health and Welfare (THL), which has received research funding from GlaxoSmithKline for a nationwide effectiveness trial of the 10-valent pneumococcal conjugate vaccine and from Pfizer and Sanofi for non-pneumococcal studies. HR-K, LS and AAP were co-investigators in the PCV10 trial. JPN, MT, and HN have no competing interests. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.08.047.

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