Impact of 13-Valent Pneumococcal Conjugate Vaccination in Invasive Pneumococcal Disease Incidence and Mortality

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Background. The impact of the 13-valent pneumococcal conjugate vaccine (PCV13) at the population level is unclear. We explored PCV13's effect in reducing invasive pneumococcal disease (IPD)–related morbidity and mortality, and whether serotype-specific changes were attributable to vaccination or expected as a part of natural, cyclical variations.

Methods. This was a Danish nationwide population-based cohort study based on the linkage of laboratory surveillance data and the Danish Civil Registration System. Changes in IPD incidence and mortality during baseline (2000–2007), 7-valent pneumococcal conjugate vaccine (PCV7) (2008–2010), and PCV13 (2011–2013) periods were estimated. Predicted incidences of serotypes were estimated controlling for cyclical trends from historical patterns observed during the past 20 years.

Results. We observed a 21% reduction (95% confidence interval [CI], 17%–25%) in IPD incidence in the total population after PCV13's introduction, and a 71% reduction (95% CI, 62%–79%) in children aged <2 years, considered as the vaccine effectiveness. We estimated a 28% reduction (95% CI, 18%–37%) in IPD-related 30-day mortality, from 3.4 deaths (95% CI, 3.2–3.6) per 100 000 population in the pre-PCV period to 2.4 (95% CI, 2.2–2.7) in the PCV13 period. The decline in mortality was observed across all age groups but was mainly related to mortality reductions in the nonvaccinated population. For serotypes 1 and 3, there were no significant changes in incidence beyond what would be expected from natural cyclical patterns. Serotype 19A significantly increased following PCV7's introduction, but the incidence declined toward baseline in 2012.

Conclusions. PCV13 has brought greater benefits than we had expected in our setting. We observed a further decline on IPD incidence shortly after the shift from PCV7 to PCV13 in the national immunization program. This decline was accompanied by a substantial population-level decline in pneumococcal-related mortality of nearly 30% among nonvaccinated persons.

Keywords. IPD; pneumococcal conjugate vaccination; incidence; mortality; indirect effect.

Pneumococcal disease continues to be one of the main public health concerns worldwide despite the availability of effective vaccines. Today, pneumococcal conjugate vaccines (PCVs) are used extensively in young children in both developed and developing countries. The 13-valent PCV (PCV13) (Prevnar 13, Pfizer) and the 10-valent pneumococcal *Haemophilus influenzae* protein D conjugate vaccine (Synflorix, GlaxoSmithKline) are widely administered as part of national and regional immunization programs, and reductions in

rates of invasive pneumococcal disease (IPD) have been demonstrated consistently in different populations [1, 2].

The 7-valent pneumococcal conjugate vaccine (PCV7) was introduced in the Danish childhood immunization program in 2007 [3] and was replaced by PCV13 during 2010 [4]. PCV7 was rapidly effective and led to approximately an 80% reduction in IPD caused by vaccine types (VT-IPD) among children <2 years of age during the first year and to a further 94% reduction in 2011 for cases of IPD due to PCV13 serotypes. An overall reduction in the rate of IPD of approximately 20% across all age groups was also observed and considered to be related to the indirect effect of the vaccine.

Despite the early successes of the programs across different countries, the increase in rates of IPD due to serotypes not included in the conjugate vaccines (non–VT-IPD) raises concern, although the magnitude of these increases following PCV7 in most populations is modest and the reported rates of non–VT-IPD varies between populations [5–7]. In contrast to PCV7, data on PCV13 vaccine effectiveness and postvaccination serotype replacement are scarce [8, 9]. Also, relatively few data regarding the effect of PCVs on mortality are currently available [1, 10–13].

We describe a sustained effect of conjugate pneumococcal vaccination 5 years after its general introduction in the national immunization program, including a significant additional decline associated with the introduction of PCV13. Moreover, the mortality rate related to IPD declined substantially and was largely driven by an indirect effect of the conjugate vaccines on disease incidence in unvaccinated adults. We also explored changes in the incidence of specific serotypes in the post-PCV7 and post-PCV13 years.

METHODS

Study Setting and Design

These analyses used data from a Danish population-based cohort study based on the linkage of national laboratory surveillance data on IPD and the Danish Civil Registration System [14]. The study was approved by the Danish Data Protection Agency (registry number 2007-41-0229).

The coverage of the Danish laboratory surveillance system based at the national Neisseria and Streptococcus Reference Laboratory, Statens Serum Institut (SSI), is high [15]. All IPD isolates were routinely serotyped at the laboratory at SSI as previously described (SSI Diagnostica, Copenhagen, Denmark) [3, 16, 17].

On 1 October 2007, PCV7 was introduced in the Danish immunization program in a 2 + 1 schedule [3]. The vaccine was administered free of charge to children aged 3, 5, and 12 months. For an initial phase, an additional 2-dose catch-up program was offered to all children between 4 and 17 months of age until 30 April 2008 [18]. Starting 19 April 2010, PCV13

gradually started to replace PCV7 [4]. The program has achieved high vaccine coverage, ranging from 79% to 92% of the 2007–2010 birth cohorts, depending on the dose [4]. The use of already existing stocks of PCV7 before starting the administration of PCV13 was recommended to general practitioners. There was no catch-up program for PCV13. We have previously defined PCV7 as a pre-PCV7 year [3, 19, 20]. Information about which PCV was given during 2010 was obtained from contact with general practitioners, and based on this information we defined 2010 as a year predominated by the use of PCV7 [20, 21]. National IPD laboratory surveillance data from 1 January 2000 to 31 December 2007 were considered as the pre-PCV period, from 1 January 2008 to 31 December 2010 as the PCV7 period, and from 1 January 2011 to 31 December 2013 as the PCV13 period. Vital status of patients was retrieved from the Danish Civil Registration System 1 month after the last patient was included in the study. Population data were obtained from Statistics Denmark (www.dst.dk).

Case Definition

A case was defined as the occurrence of IPD in a patient from whom *Streptococcus pneumoniae* was isolated from cerebrospinal fluid (CSF), blood, or other sterile site as previously described [3, 19, 20]. Death was considered as likely to be related with IPD when the date of death was registered within 30 days after the clinical sample was obtained.

Estimates of Vaccine Effectiveness

The impact of introducing PCV7 in the childhood vaccination program was estimated based on changes in the number of laboratory-confirmed IPD cases per 100 000 population. Serotypes included in PCV7 are 4, 6B, 9V, 14, 18C, 19F, and 23F. Additional PCV13 serotypes are 1, 3, 5, 6A, 7F, and 19A. All other serotypes were categorized as non-VT serotypes. Serotypes unique to the 23-valent pneumococcal polysaccharide vaccine (PPSV23) formulation are 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F. Changes in incidence and mortality rates were assessed by comparing ratios (incidence rate ratios [IRRs] and mortality rate ratios) with 95% confidence intervals (CIs) using Poisson regression (Stata Statistical Software, version 9.2; StataCorp, College Station, Texas) and SAS Software, version 9.1 (SAS Institute, Cary, North Carolina). Vaccine effectiveness was calculated as $(1 -$ incidence rate$) \times 100\%$. Proportions were compared using χ^2 or Fisher exact test when appropriate. Two-tailed P values <.05 were considered statistically significant.

Serotype Specific Trends Over Time

We explored whether there was an indirect effect of PCV13 against PCV13 serotypes in adults while looking at trends of individual serotypes. Because cyclical variations in the incidence of serotypes have been described in our population [19], we

explored whether the observed postvaccination changes were attributable to the vaccine or were part of the regular cyclical variation. We used serotype-specific data from 1993 to 2013 to control for these variations over a longer time period [19]. We used 3 different models to test whether the changes in incidence of chosen serotypes observed in the post-PCV13 period (2011–2013) were greater than would be expected from the historical patterns. Model 1 is a simple comparison of the average for 2011–2013 vs the average for 1993–2007. Model 2 controls for linear trend when comparing the 2 periods. Model 3 controls for a linear trend and 7-year cycles (previously seen as natural trends) when comparing the 2 periods (using sine and cosine terms with a 7-year period). The models were fit in SAS version 9.3 using PROC GENMOD (Poisson distribution, log link). The model with the lowest Akaike information criterion score was considered best; we also considered models with harmonic terms with periods of 4–10 years. For extrapolations, the models were fit to data through 2007. Prediction intervals were calculated as previously described [22]. The graphs showing the predicted incidence of serotypes were drawn in the statistical software R (available at: http://www.r-project.org/) [23].

RESULTS

Changes in Incidence Rates

The total number of IPD cases tended to decline, from 1056 cases per year (range, 823–1232) in the pre-PCV period to 988 cases per year (range, 938–1050) during the PCV7 period and to 869 cases per year (range, 820–912) during the PCV13 period. Approximately 90% of isolates were obtained from blood; 5%–10% from CSF and <1% from other sterile sites. The proportion of isolates obtained from those sterile foci did not change over the study period.

The overall incidence of IPD declined significantly with estimated overall reduction of 21% (IRR, 0.79 [95% CI, .76–.83]; Figure 1A, Table 1). The decrease in the incidence of IPD caused by all serotypes fell markedly in children aged <2 years, corresponding with an estimated 71% reduction (IRR, 0.29 [95% CI, .21–.37]) in the PCV13 period compared with baseline, considered as the vaccine effectiveness. The incidence tended to decline across other age groups but mainly in young children (Figure 1B).

The overall incidence of laboratory-confirmed pneumococcal meningitis cases also declined by nearly a third of cases between the PCV13 and pre-PCV periods (PCV7 vs pre-PCV: IRR, 0.82 [95% CI, .70–.96]; PCV13 vs PCV7: IRR, 0.79 [95% CI, .64–.97]; PCV13 vs pre-PCV: IRR, 0.64 [95% CI, .54–.76]). The decline was significant in children aged <2 years (PCV7 vs pre-PCV: IRR, 0.52 [95% CI, .33–.79]; PCV13 vs PCV7: IRR, 0.50 [95% CI, .24–1.01]; PCV13 vs pre-PCV: IRR, 0.26 [95% CI, .13–.46]). However, meningitis rates did not
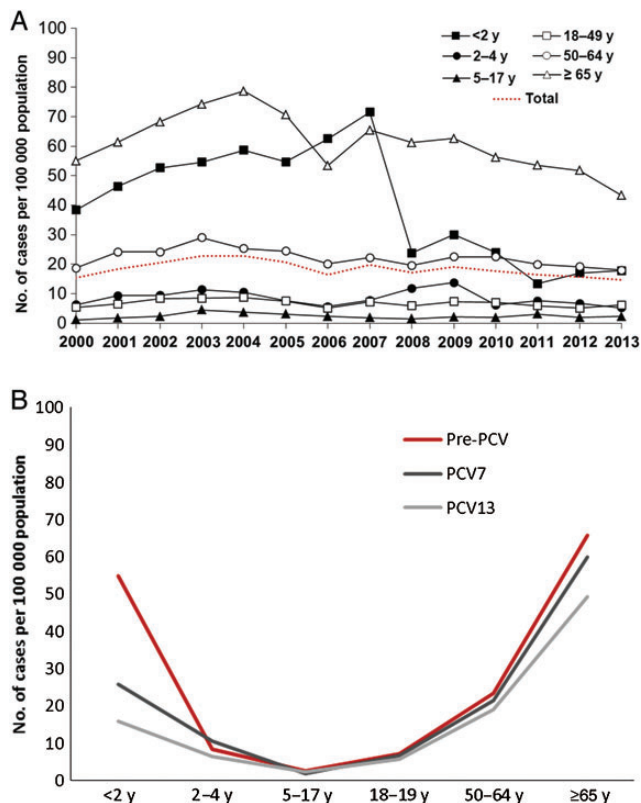

Figure 1. *A*, Incidence of invasive pneumococcal disease (IPD) in Denmark, 2000–2013. The figure shows the annual number of laboratory-confirmed IPD cases per 100 000 population, stratified by age group. The heptavalent pneumococcal conjugate vaccine (PCV7) was introduced in October 2007 and was slowly replaced by the currently available 13-valent pneumococcal conjugate vaccine (PCV13) starting April 2010. *B*, Changes in estimated age-specific incidence of IPD after the introduction of conjugate vaccination in the national immunization program during the pre-PCV (2000–2007), PCV7 (2007–2010), and PCV13 periods (2011–2013). The shape of the IPD incidence curve has changed remarkably after PCV's introduction, with a marked decline of IPD in young children but still remaining high in the elderly. Abbreviations: PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; Pre-PCV, pre-pneumococcal conjugate vaccine.

significantly decline in the other age groups, including adults aged ≥65 years where the highest incidence of the disease is observed (PCV7 vs pre-PCV: IRR, 1.03 [95% CI, .77–1.36]; PCV13 vs PCV7: IRR, 0.80 [95% CI, .59–1.07]; PCV13 vs pre-PCV: IRR, 0.77 [95% CI, .541–1.09]).

Effect of PCV7 and PCV13 on the Distribution and Incidence of Serotypes

In children <2 years (Figure 2A, Table 2), the incidence of the 6 additional PCV13 serotypes decreased, with an estimated 84% reduction (IRR, 0.16 [95% CI, .07–.33]) of IPD caused by these serotypes. In the population aged ≥65 years (Figure 2B, Table 2), the incidence of PCV7 serotypes declined significantly, with an estimated approximately 88% reduction in IPD due to PCV7

Table 1. Changes in Incidence Rate Among Cases of Invasive Pneumococcal Disease at Baseline (Pre–Pneumococcal Conjugate Vaccine [PCV], 2000–2007) and After the Introduction of PCV7 (2008–2010) and PCV13 (2011–2013), Denmark

| | Incidence | | | | | | IRR | | |
| | Pre-PCV | | PCV7 | | PCV13 | | PCV7 vs Pre-PCV | PCV13 vs PCV7 | PCV13 vs Pre-PCV |
Age Group	No.	IR	No.	IR	No.	IR			
<2	578	55.1 (50.8–59.8)	101	25.9 (21.3–31.5)	59	16.0 (12.4–20.6)	0.47 (.37–.58)	0.61 (.43–.85)	0.29 (.21–.37)
2–4 y	135	8.4 (7.1–10.0)	62	10.5 (8.2–13.5)	38	6.8 (5.0–9.3)	1.25 (.91–1.70)	0.61 (.39–.93)	0.76 (.52–1.10)
5–17 y	174	2.5 (2.2–2.9)	50	1.9 (1.4–2.5)	64	2.4 (1.9–3.1)	0.73 (.52–1.01)	1.29 (.87–1.90)	0.95 (.70–1.27)
18–49 y	1338	7.1 (6.8–7.5)	471	6.8 (6.2–7.4)	400	5.7 (5.2–6.5)	0.94 (.85–1.05)	0.84 (.73–.96)	0.80 (.71–.89)
50–64 y	1973	23.6 (22.5–24.6)	706	21.6 (22.0–23.2)	612	19.0 (17.5–20.6)	0.91 (.83–.99)	0.88 (.78–.98)	0.80 (.73–.88)
≥65 y	4227	65.5 (63.6–67.5)	1580	60.0 (57.2–63.1)	1434	49.4 (46.9–52.0)	0.91 (.86–.97)	0.82 (.76–.88)	0.75 (.70–.80)
Overall	8425	19.5 (19.1–20.0)	2970	18.0 (17.3–18.6)	2607	15.6 (15.0–16.2)	0.91 (.88–.95)	0.86 (.82–.91)	0.79 (.76–.83)

Estimates represent number of cases per 100 000 population (95% confidence interval); IRRs were calculated to express differences in rates.
Abbreviations: IR, incidence rate; IRR, incidence rate ratio; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; Pre-PCV, pre-pneumococcal conjugate vaccine.

serotypes. The proportion of IPD cases in this age group caused by PCV13 serotypes slightly increased from 28% in the pre-PCV period to 34% in the PCV13 period. The proportion of serotypes unique to PPSV23 in adults aged ≥65 years increased

Figure 2. Incidence of vaccine-type invasive pneumococcal disease (VT-IPD) by age group, Denmark, 2000–2013. VT-IPD includes serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F; additional 13-valent pneumococcal conjugate vaccine (PCV13) serotypes are 1, 3, 5, 6A, 7F, and 19A. All other serotypes were considered as non-PCV7/PCV13 serotypes. Abbreviations: PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

significantly, from 24% to 30% to 35% in the pre-PCV, PCV7, and PCV13 periods, respectively (*P* < .001). Also, the incidence of serotypes unique to PPSV23 increased significantly in all age groups (Table 2). Serotypes 8, 9N, 12F, and 22F represented 70% of the cases caused by only PPSV23 serotypes.

In children aged <2 years, PCV7 serotypes have virtually disappeared; only 1 case of 19F pneumococcal bacteremia was observed in 2011 (in an unvaccinated, immunocompromised child), and no cases were observed in 2012 and 2013. After the introduction of PCV13, cases of IPD due to the additional PCV13 serotypes were diagnosed in 7 nonvaccinated children (2 cases of serotype 1 IPD, 3 cases of serotype 7F IPD, and 2 cases of serotype 3 IPD). One additional case of serotype 3 bacteremic pneumonia occurred in a child who had previously received 2 doses of PCV13. The immunologic status of this patient is under investigation, but no clinical signs of immunosuppression were present before the IPD-related admission. Nearly 80% of cases in 2012–2013 were caused by non–VT-IPD (8, 10A/B, 12F, 15B/C, 20, 22F, 33F, 38, 23B, 24F), with no clear predominance of any specific serotype.

Only serotypes 1, 3, and 19A tended to remain constant or increased after the introduction of PCV13 (Table 2, Figure 3). For serotypes 1 and 3, there were no significant changes in incidence beyond what would be expected from the natural cyclical patterns. Therefore, there was no evidence of serotype replacement for these serotypes following PCV7, but there was no evidence of vaccine impact following PCV13. Serotype 1 and 3 both showed evidence of 7-year cyclical variations, and controlling for these variations when estimating the post-PCV13 vaccine impact resulted in IRR estimates close to 1 (serotype 1 IRR, 1.03 [95% CI, .88–1.23]; serotype 3 IRR, 1.08 [95% CI, .83–1.41]). For serotype 19A, there was a significant increase in disease incidence following PCV7, and by 2012, there was
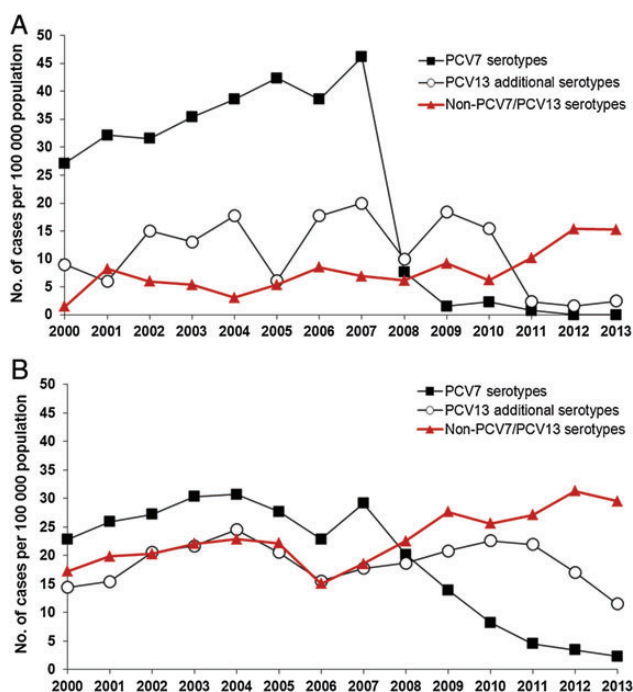
Table 2. Incidence of Invasive Pneumococcal Disease Caused by Vaccine Serotypes During the Pre–Pneumococcal Conjugate Vaccine (PCV) Period (2000–2007), PCV7 Period (2008–2010), and PCV13 Period (2011–2013), Denmark

	Children <2 y			Adults ≥65 y		
Serotypes	Pre-PCV	PCV7	PCV13	Pre-PCV	PCV7	PCV13
PCV7 serotypes						
4	1.9 (1.2–2.9)	. . .	. . .	6.2 (5.7–6.9)	3.2 (2.5–3.9)	1.1 (.8–1.5)
6B	10.7 (8.9–12.8)	1.3 (.5–3.0)	. . .	2.4 (2.0–2.8)	1.2 (.8–1.7)	0.3 (.1–.6)
9V	2.1 (1.4–3.1)	0.3 (.04–1.8)	. . .	4.3 (3.8–4.8)	2.2 (1.7–2.9)	0.1 (.1–.4)
14	11.8 (9.9–14.1)	0.8 (.2–2.4)	. . .	8.2 (7.5–8.9)	3.5 (2.8–4.2)	0.5 (.3–.9)
18C	2.3 (1.5–3.4)	0.5 (.1–2.0)	. . .	0.7 (.5–.9)	1.0 (.7–1.5)	0.3 (.1–.6)
19F	4.0 (2.9–5.4)	1.0 (.4–2.7)	0.3 (.03–1.9)	2.1 (1.8–2.5)	1.4 (1.1–2.0)	0.8 (.5–1.2)
23F	3.6 (2.6–4.9)	0.3 (.03–1.8)	. . .	3.2 (2.8–3.6)	1.5 (1.1–2.0)	0.2 (.1–.5)
All PCV7	36.4 (32.9–40.3)	3.9 (2.3–6.4)	0.3 (.03–1.9)	27.1 (25.8–28.4)	14.0 (12.6–15.5)	3.3 (2.7–4.0)
Additional PCV13 serotypes						
1	1.6 (1.0–2.6)	1.3 (.5–3.0)	0.5 (.1–2.2)	6.0 (5.4–6.6)	6.0 (5.1–7.0)	6.1 (5.2–7.0)
5	0.3 (.09–.9)	0.3 (.03–1.8)	. . .	0.3 (.2–.5)	0.1 (.02–.3)	0.03 (.005–.24)
7F	4.9 (3.8–6.5)	6.9 (4.7–10.1)	0.8 (.3–2.5)	4.7 (4.2–5.3)	5.5 (4.7–6.5)	3.0 (2.4–3.7)
3	0.6 (.2–1.3)	1.3 (.5–3.0)	0.8 (.3–2.5)	4.2 (3.7–4.7)	4.4 (3.6–5.2)	4.5 (3.8–5.4)
6A	4.3 (3.2–5.7)	1.3 (.5–3.0)	. . .	2.0 (1.7–2.4)	1.5 (1.1–2.0)	0.3 (.1–.6)
19A	1.3 (.8–2.2)	3.8 (2.3–6.3)	. . .	1.6 (1.3–1.9)	3.3 (2.6–4.0)	2.9 (2.3–3.5)
All additional	13.1 (11.0–15.4)	14.4 (11.1–18.7)	2.2 (1.1–4.3)	18.8 (17.7–19.9)	20.7 (19.0–22.5)	16.9 (15.4–18.4)
Non-VT	5.6 (4.3–7.2)	7.2 (4.9–10.5)	13.5 (10.2–17.8)	19.7 (18.7–20.8)	25.3 (23.5–27.3)	29.4 (27.5–31.4)
Only PPSV23	3.1 (2.2–4.4)	3.3 (1.9–5.7)	7.0 (4.8–10.4)	15.2 (14.3–16.2)	18.2 (16.6–19.9)	18.9 (17.4–20.6)

Incidences are shown for PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, 29F, 23F), additional serotypes included in PCV13 (1,5,7F, 3, 6A, 19A), all non-VT serotypes, and only serotypes unique to PPSV23. Estimates represent the number of cases per 100 000 population (95% confidence interval).

Abbreviations: PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, pneumococcal polysaccharide vaccine; Pre-PCV, pre-pneumococcal conjugate vaccine; VT, vaccine type.

evidence that the incidence was declining toward baseline pre-PCV7 levels. There was no evidence of consistent epidemic cycles for serotype 19A, so simple comparisons of the incidence rates between periods provided the best estimates.

IPD-Related Mortality in the Pre-PCV, PCV7, and PCV13 Periods

Survival status of patients after 14 002 IPD episodes was ascertained. The mean 30-day case mortality proportion after IPD ranged between 15% and 17%, irrespective of the period (Table 3). The overall mortality rate declined approximately in 28% (95% CI, 18%–27%; Table 3). The decline in mortality rate was significant only for the population aged ≥5 years. In children <5 years, mortality was very low, ranging from 0 to 2 cases per year (0%–2%), and tended to decline during the PCV7 period compared with the pre-PCV period, although these differences in rates were not statistically significant.

DISCUSSION

We have seen a rapid and sustained reduction in IPD, 5 years after the introduction of the first pneumococcal conjugate vaccine in Denmark, with an additional benefit of PCV13 compared with PCV7. Furthermore, we observed a significant

reduction in the overall mortality related to IPD in the nonvaccinated population.

Our estimates on PCV13's vaccine effectiveness are encouraging, reaching an approximately 85% reduction in the incidence of the 6 additional PCV13 serotypes and approximately 71% for IPD caused by all serotypes in children aged <2 years, somewhat higher than the 57% reported from the United States and similar to the 78% reported from a United Kingdom study during the early post-PCV13 period [8, 9]. The increasing incidence of serotype 19A has been documented after the introduction of PCV7 [20, 24], a phenomenon we also observed. Serotype 19A cases peaked in 2010 (3 years after PCV7 introduction) and declined by 50% by 2012 (2 years following PCV13 introduction), so in our cohort, PCV13 led to an early and rapid decline in the proportion of 19A-IPD. Although we have observed a significant increase in the incidence of non–VT-IPD, no other serotypes have emerged similarly to 19A after PCV13's introduction, in contrast to what has, for example, been recently described in Norway [25].

The rates of IPD among all age groups tended to decline, although the effect is clearer in bacteremia cases compared to meningitis. In persons aged ≥65 years, significant changes in
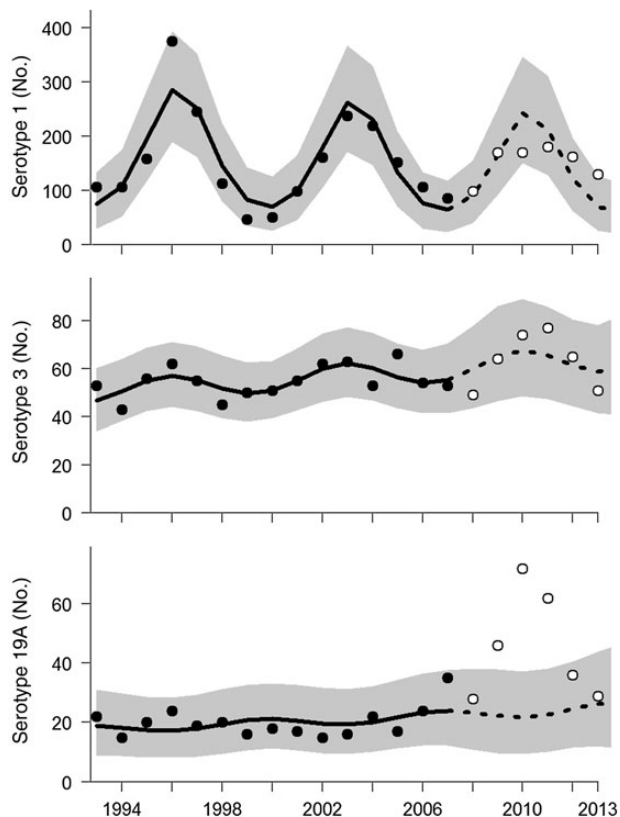
Figure 3. Trends of individual vaccine serotypes before and after the introduction of conjugate vaccines in Denmark, 1993–2013. The graphs show the number of cases of invasive pneumococcal disease caused by serotypes 1, 3, and 19A in the total population. The black dots represent the observed number of cases before the introduction of 7-valent pneumococcal conjugate vaccine (PCV7; 2007) and 13-valent pneumococcal conjugate vaccine (PCV13; 2010); the white dots, after the introduction of the vaccines. The solid line shows the estimate incidence in each year, calculated from the trend analysis, and the dashed line shows the predicted number of cases for the post-PCV7 and -PCV13 years, as estimated by the trend analysis.

serotype distribution also occurred and are likely attributable to the indirect effect of conjugate vaccination. In the PCV13 period, only 6% of IPD cases in this age group were caused by PCV7 serotypes, compared with 41% in the pre-PCV period. In contrast, non-PCV13 serotypes accounted for 59% of cases in the PCV13 period, compared with 30% in the pre-PCV period. These results are important in the light of the current debate regarding recommendations on pneumococcal vaccination of adults and the most appropriate vaccine to choose. In the near future, it is not unlikely that universal vaccination of adults with PCV13 may be less relevant from a public health point of view, due to the indirect effect of infant vaccination on the overall serotype distribution of IPD cases in the population, whereas PPSV23 would still provide an advantage in serotype coverage for adults. Other considerations related to the immunogenicity of the vaccines and their effect on pneumonia cases are also important and have to be considered at the individual patient level. Our results underline the continuing relevance of PPSV23 vaccination in a setting of evolving serotype epidemiology in the framework of pneumococcal conjugate vaccination.

Most of the reduction in mortality rates occurred in the population aged >18 years. In our cohort, more than two-thirds of bacteremic cases have been reported to be related to a pneumonia hospital admission [11], which is a leading cause of deaths among adults [12, 13]. The decline was statistically significant and not explained by an increase in vaccination coverage in adults with PPSV23. However, there has been an increase in the private sales of PCV13 (outside the national immunization program), from 0 doses in 2011 to 1478 doses in 2013 (unpublished data, Sales and Business Development Department, SSI). This increase could be related to the introduction of a limited subsidy to cover pneumococcal vaccination of persons at increased risk of IPD by the Danish Health and Medicines

Table 3. Changes in 30-Day Mortality Rates Among Patients With Invasive Pneumococcal Disease at Baseline (Pre–Pneumococcal Conjugate Vaccine [PCV], 2000–2007) and After the Introduction of PCV7 (2008–2010) and PCV13 (2011–2013), Denmark

| Age Group | Mortality | | | | | | MRR | | |
| | Pre-PCV | | PCV7 | | PCV13 | | PCV7 vs Pre-PCV | PCV13 vs PCV7 | PCV13 vs Pre-PCV |
	No.	MR	No.	MR	No.	MR			
<2	14	1.3 (.8–2.3)	1	0.3 (.03–1.8)	1	0.4 (.04–1.9)	0.19 (.004–1.26)	1.55 (.019–121.8)	0.29 (.0007–1.96)
2–4 y	1	0.1 (.01–.4)	0	...	0	...	...	...	...
5–17 y	4	0.1 (.02–.2)	0	...	0	...	...	...	...
18–49 y	115	0.6 (.5–.7)	27	0.4 (.3–.6)	17	0.4 (.2–.5)	0.63 (.39–.96)	0.93 (.48–1.78)	0.59 (.33–.99)
50–64 y	322	3.8 (3.4–4.3)	88	2.7 (2.2–3.3)	54	2.5 (2.1–3.2)	0.69 (.54–.88)	0.93 (.65–1.32)	0.65 (.47–.87)
≥65 y	998	15.4 (14.5–16.5)	393	14.9 (13.6–16.5)	200	10.5 (8.5–10.7)	0.95 (.85–1.08)	0.70 (.59–.83)	0.67 (.58–.79)
Overall	1452	3.4 (3.2–3.6)	509	3.1 (2.8–3.4)	272	2.4 (2.2–2.7)	0.91 (.82–1.00)	0.79 (.68–.91)	0.72 (.63–.82)

Estimates represent number of deaths per 100 000 population (95% confidence interval); MRRs were calculated to express differences in rates.

Abbreviations: MR, mortality rate; MRR, mortality rate ratio; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; Pre-PCV, pre-pneumococcal vaccine.

Authority starting from 29 October 2012 [26]. The decline in mortality rates related to IPD was accompanied by a drop in VT-IPD rates and was more accentuated in the elderly. Simultaneously, serotype-specific case-fatality proportions remained quite stable from baseline to the PCV7 and PCV13 periods, but as pointed out by previous studies, this can be considered to be a serotype-specific characteristic [11, 27]. In particular, in the case of pneumococcal disease, a decline in population mortality after vaccination would not necessarily be expected, as the changes in serotype distribution with higher prevalence of non–VT-IPD could have led to higher severity of disease in the population, as indicated by other studies. These observations support the hypothesis that the observed changes in mortality trends are likely attributable to the indirect benefits of the vaccine.

The results of several exploratory models suggested that vaccination so far has had little effect on the incidence of serotypes 1 and 3 IPD. We have previously described that both cyclical and secular trends are characteristic for those serotypes [19]. There are, however, caveats to these estimates, including the fact that we used raw counts and not incidences, that the estimates are not age-stratified, and that the methods used were conservative, resulting in wide limits of the CI.

In a broader context, our results speak to the potential benefits of conjugate vaccination in resource-limited settings, in particular through the vaccines' contribution to mortality decline. Naturally, the impact of a PCV in pneumococcal disease mortality will probably vary among different populations, related to factors such as ethnicity, the prevalence of comorbidities, age, social conditions, and access to healthcare. More data from different settings are needed to assess this topic.

Our study has a number of strengths, including complete information on serotypes and vaccination status of children aged <5 years, and a solid national population-based surveillance system. Also, preliminary data for individual communities/regions in the country indicate that no major changes in CSF or blood culturing practices have occurred during the study period (data not shown). Among the limitations, we can mention that the case definition was highly specific and limited to include culture-confirmed cases. Also, blood and CSF cultures are almost exclusively obtained in hospital settings in Denmark, both factors contributing to underestimation in incidence rates. The decrease in cases among adults may thus be related to other factors than the introduction of pneumococcal conjugate vaccination, such as admission rates following influenza outbreaks [11, 28]. However, such variations would be expected to occur over short time periods and would not influence long-term trends. Also, we did not adjust for comorbidities of patients, which are important risk factors for susceptibility and mortality after IPD.

In summary, we found that PCV13 in a 2 + 1 infant immunization schedule has led to a further reduction of morbidity and mortality in both vaccinated and nonvaccinated persons in Denmark. These results are important for understanding and rethinking immunization policies for both developing and industrialized countries.

Notes

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