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Twelve years of pneumococcal conjugate vaccination in the Netherlands: Impact on incidence and clinical outcomes of invasive pneumococcal disease

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ABSTRACT

Introduction: In 2006, the Netherlands introduced the 7-valent pneumococcal conjugate vaccine (PCV7) in their national immunisation programme. In 2011, PCV7 was replaced by the 10-valent vaccine (PCV10). We report on the impact of PCV on invasive pneumococcal disease (IPD) incidence, clinical syndromes and patient outcomes.

Methods: Pneumococcal isolates of hospitalised IPD patients between June 2004 and May 2018 were obtained from nine sentinel laboratories, covering 25% of the Dutch population. All isolates were serotyped. IPD incidence and clinical outcome were determined before and after introduction of PCV7 and after the switch to PCV10, stratified by age and serotype.

Results: Compared to before PCV7 introduction, significant declines in IPD incidence were observed in 2016–2018 in children <5 years (69%), 18–49 year olds (31%) and ≥65 year olds (19%). Compared to before PCV10 introduction, the IPD incidence in 2016–2018 declined in children <5 years (RR:0.68, 95% CI:0.42–1.11), 5–17 year olds (RR:0.58, 95%CI:0.29–1.14) and 18–49 year olds (RR:0.72, 95%CI:0.57–0.90), but not in 50–64 year olds (RR:0.94, 95%CI:0.81–1.10) and ≥65 year olds (RR:1.04, 95%CI:0.0.93–1.15). While the case fatality rate (CFR) decreased from 16.2% pre-PCV to 13.4% post-PCV10 (RR:0.83, 95%CI:0.70–0.99), the switch to PCV10 had no further impact on CFR (RR:1.14, 95%CI:0.96–1.36).

Conclusion: Twelve years of PCV in the Netherlands has resulted in a sustained reduction of IPD incidence in children and younger adults. The switch from PCV7 to PCV10 did not have additional impact on the IPD incidence in older adults and CFR due to emerging non-vaccine serotypes.

1. Introduction

Invasive pneumococcal disease (IPD) is associated with high morbidity and mortality worldwide [1,2]. IPD is defined as an infection of a normally sterile body fluid, typically blood or cerebrospinal fluid (CSF), by the gram-positive bacterium *Streptococcus pneumoniae*, with clinical syndromes including septicaemia, invasive pneumonia or meningitis.

Currently available vaccines are the 10- and 13-valent pneumococcal conjugate vaccines (PCV) and the 23-valent pneumococcal polysaccharide vaccine (PPV23). As of September 2018, 145 countries worldwide have implemented PCV in their national immunisation programme for infants [3,4]. In the Netherlands, the 7-valent pneumococcal conjugate vaccine (PCV7) was introduced in 2006, and was replaced by PCV10 in 2011. PCV coverage in children at age 2 years has been 93–95% since the introduction of PCV7 [5]. Up to 2018, PPV23 has been recommended only for those at high risk for IPD, and PPV23 use has been very low in the Netherlands (<0.5% of persons ≥65 years in 2017) [6,7].

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Four years after the introduction of PCV7, the overall IPD incidence in Dutch children under two years had decreased by 57% and, due to indirect protection, by 22% in adults ≥65 years [8]. Three years after the switch to PCV10, a further reduction in IPD incidence of 30% was observed in children under 2 years. In adults ≥65 years, a decline in IPD caused by the additional PCV10 serotypes 1, 5 and 7F of 25% was observed, but the overall IPD incidence plateaued; this was attributed to a steady rise of non-PCV10 serotypes [8,9]. In England and Wales, replacement disease from non-PCV13 serotypes, in particular serotypes 8, 12F and 9N, has progressively eroded the IPD reduction in older adults; in 2016–2017 almost no net benefit was observed from the PCV7 to PCV13 switch [10].

The aim of the current study was to describe the overall impact since PCV7 introduction in 2006, and in particular the impact of the switch from PCV7 to PCV10 in 2011 on IPD incidence, clinical syndromes and patient outcomes in the Netherlands.

2. Methods

2.1. Study population and data collection

Since 2004, national IPD surveillance in the Netherlands is based on data from nine sentinel clinical microbiological laboratories which submit pneumococcal isolates to the Netherlands Reference Laboratory for Bacterial Meningitis for serotyping by agglutination and subtyping by the Quellung method [11]. IPD was defined as identification of *S. pneumoniae* isolated from the patient's blood or CSF. The sentinel laboratories cover ~25% of the Dutch population and coverage has not changed since 2004 [12,13]. Clinical information on IPD patients, including clinical syndrome and course of disease, was extracted retrospectively from hospital medical records using a standardised form with study procedures as previously reported. IPD serotype data from June 2004 to May 2018 (i.e. using epidemiological years) are included in the current analysis. Clinical data were available from June 2004 to May 2016. The independent Medical Research Ethics Committee of the UMC Utrecht has determined that the study (protocol number 16–256/C) is not subject to the Medical Research Involving Human Subjects Act (WMO).

2.2. Clinical characteristics and definitions

We applied the same definitions for clinical syndromes and outcomes as in previous surveillance reports [9]. Five clinical IPD syndromes were defined: meningitis, invasive pneumonia with empyema, invasive pneumonia without empyema, bacteraemia with another and bacteraemia without a focus. Empyema assessment was based on clinical and/or radiographic evaluation. Death was defined as deceased during admission or within 30 days after obtaining the *S. pneumoniae* culture-positive material. Observations with missing values were excluded. Underlying conditions were divided into immunocompromising and non-immunocompromising comorbidities, as reported previously [9].

2.3. Data analyses

Incidence of IPD was calculated as number of cases per 100,000 persons per epidemiological year, taking into account the coverage of the surveillance programme (25% of the Dutch population). IPD incidence in the last two epidemiological years (June 01, 2016 to May 31, 2018) was compared to the two epidemiological years before PCV7 introduction (June 01, 2004 to May 31, 2006) and PCV10 introduction (June 01, 2009 to May 31, 2011). Two-year periods were chosen instead of one year to reduce the impact of temporal variations. Incidence was stratified by age groups (<5, 5–17, 18–49, 50–64, ≥65 years) and/or by four serotype groups: PCV7 type (4, 6B, 9V, 14, 18C, 19F, 23F); PCV10-7 type (1, 5, 7F), PCV13-10 type (3, 6A and 19A) and non-PCV13 type (all other serotypes).

Clinical syndromes, ICU admission and case fatality rate (CFR) were compared between three periods: pre-PCV (June 01, 2004 to May 31, 2006), post-PCV7 (June 01, 2008 to May 31, 2011) and post-PCV10 (June 01, 2013 to May 31, 2016). The first two epidemiological years after PCV7 and PCV10 introduction were disregarded, since herd protection was not yet expected to be observed [13]. Note that the periods for clinical data analyses are slightly different from the periods used for the IPD incidence analyses because of data availability and sample size considerations. The same age and serotype group strata as for the incidence data were applied.

Baseline differences in patient characteristics between time periods were tested using independent sample t-tests or $\chi 2$, where appropriate. Differences in incidences and proportions between the time periods were tested with $\chi 2$ tests and RRs with 95% CI were calculated. A p-value of <0.05 was considered to represent a statistically significant difference. If considered appropriate, multivariable logistic regression analyses were performed to adjust for age and/or comorbidities when assessing associations between time periods and outcomes.

3. Results

3.1. IPD incidence (June 2004 to May 2018)

A total of 8865 IPD patients were identified between June 2004 and May 2018. Compared with the pre-PCV period, the overall incidence of IPD in 2016–2018 across all age groups had not declined significantly (RR: 0.94, 95%CI: 0.87–1.02) (Table 1, Fig. 1). There was, however, a statistically significant decline in IPD incidence in children <5 years (69%), in 18–49 year olds (31%) and in persons ≥65 years (19%). After the switch from PCV7 to PCV10, a continuous decline in overall IPD incidence was observed in age groups below 50 years; this was statistically significant only in the 18–49 years age group, whereas overall IPD incidence showed no (further) reduction in 50–64 year-olds and in persons ≥65 years. Subdividing the IPD cases among persons ≥65 years into smaller groups shows a very similar trend in each group (Supplementary Table S1 and Fig. S1).

Between 2004 and 2006 and 2016–2018, PCV7 type IPD has declined by 90–100% in all age groups. After the switch to PCV10, the incidence of PCV10-7 type IPD (serotypes 1, 5 and 7F) also declined in all age groups, with 91% reduction in children under 5 years and 72–76% reduction in adult age groups by 2016–2018 (Table 1). The incidence of PCV13-10 type IPD (serotypes 3, 6A and 19A) increased by 44% after PCV10 introduction, and by 97% over the whole period between 2004 and 2006 and 2016–2018; this increase was apparent in all adult age groups, though only statistically significant in the age groups 50–64 years and ≥65 years. Serotype 6A IPD incidence declined substantially after PCV7 introduction, due to cross reactivity with PCV7 serotype 6B. Serotype 19A IPD incidence increased significantly from 0.5 per 100,000 in 2004–2006 to 1.4 per 100,000 in 2009–2011 and 2.0 per 100,000 in 2016–2018 (Fig. 2). Serotype 3 IPD incidence increased significantly after the switch to PCV10, from 0.9 per 100,000 in 2009–2011 to 1.4 per 100,000 in 2016–2018. In 2016–2018, serotypes 19A and 3 were the second and third most common IPD-causing serotypes in the Netherlands. In 2016–2018, the non-PCV13 IPD incidence had increased by 65%-160% in adult age groups compared with 2004–2006. This was primarily due to the

Table 1
Incidence (per 100,000) and relative risks of IPD incidence comparing June 2016–May 2018 with the two years before PCV introduction (June 2004 to May 2006) and the two years before PCV10 introduction (June 2009 to May 2011) by age group and serotype group.

Age	Serotype group	2004–2006		2009–2011		2016–2018		2016–2018 vs. 2004–2006		2016–2018 vs. 2009–2011	
		Incidence (/100,000)	N	Incidence (/100,000)	N	Incidence (/100,000)	N	RR	95% CI	RR	95% CI
<5 years	PCV7	13.48	68	0.65	3	0.69	3	0.05	0.02–0.16	1.06	0.21–5.25
	PCV10-7	2.38	12	2.59	12	0.23	1	0.10	0.01–0.74	0.09	0.01–0.68
	PCV13-10	2.18	11	1.73	8	1.60	7	0.74	0.28–1.90	0.93	0.34–2.56
	Non-PCV13	1.78	9	4.10	19	3.66	16	2.05	0.91–4.65	0.89	0.46–1.74
	Total	**19.82**	**100**	**9.07**	**42**	**6.18**	**27**	**0.31**	**0.20–0.48**	**0.68**	**0.42–1.11**
5–17 years	PCV7	0.85	11	0.46	6	0.00	0	0.00	NA	0.00	NA
	PCV10-7	0.39	5	0.93	12	0.16	2	0.41	0.08–2.10	0.17	0.04–0.76
	PCV13-10	0.00	0	0.23	3	0.16	2	NA	NA	0.68	0.11–4.08
	Non-PCV13	0.46	6	0.15	2	0.71	9	1.53	0.55–4.30	4.60	0.99–21.28
	Total	**1.70**	**22**	**1.78**	**23**	**1.03**	**13**	**0.60**	**0.30–1.20**	**0.58**	**0.29–1.14**
18–49 years	PCV7	1.71	63	0.97	35	0.17	6	0.10	0.04–0.23	0.18	0.07–0.42
	PCV10-7	1.87	69	2.17	78	0.52	18	0.28	0.16–0.46	0.24	0.14–0.40
	PCV13-10	0.33	12	0.58	21	0.60	21	1.85	0.91–3.76	1.03	0.56–1.89
	Non-PCV13	1.44	53	1.39	50	2.38	83	1.65	1.17–2.34	1.71	1.20–2.43
	Total	**5.35**	**197**	**5.12**	**184**	**3.67**	**128**	**0.69**	**0.55–0.86**	**0.72**	**0.57–0.90**
50–64 years	PCV7	7.88	120	3.19	53	0.45	8	0.06	0.03–0.12	0.14	0.07–0.30
	PCV10-7	2.82	43	4.99	83	1.25	22	0.44	0.26–0.74	0.25	0.16–0.40
	PCV13-10	2.63	40	3.06	51	4.81	85	1.83	1.26–2.67	1.57	1.11–2.22
	Non-PCV13	4.60	70	8.35	139	11.95	211	2.60	1.98–3.41	1.43	1.15–1.77
	Total	**17.92**	**273**	**19.59**	**326**	**18.47**	**326**	**1.03**	**0.88–1.21**	**0.94**	**0.81–1.10**
≥65 years	PCV7	30.09	344	8.85	112	2.55	40	0.08	0.06–0.12	0.29	0.29–0.41
	PCV10-7	10.06	115	9.01	114	2.49	39	0.25	0.17–0.36	0.28	0.19–0.40
	PCV13-10	7.35	84	9.64	122	11.98	188	1.63	1.26–2.11	1.24	0.99–1.56
	Non-PCV13	15.22	174	21.65	274	33.97	533	2.23	1.88–2.65	1.57	1.36–1.81
	Total	**62.72**	**717**	**49.16**	**622**	**50.99**	**800**	**0.81**	**0.74–0.90**	**1.04**	**0.93–1.15**
All ages	PCV7	7.44	606	2.52	209	0.67	57	0.09	0.07–0.12	0.26	0.20–0.36
	PCV10-7	2.99	244	3.61	299	0.96	82	0.32	0.25–0.41	0.27	0.21–0.34
	PCV13-10	1.80	147	2.47	205	3.55	303	1.97	1.62–2.40	1.44	1.20–1.71
	Non-PCV13	3.83	312	5.84	484	9.99	852	2.61	2.29–2.97	1.71	1.53–1.91
	Total	**16.06**	**1309**	**14.45**	**1197**	**15.18**	**1294**	**0.94**	**0.87–1.02**	**1.05**	**0.97–1.14**

Abbreviations: CI, confidence interval; NA, not applicable; PCV, pneumococcal conjugate vaccine, N, number of cases.

rapid emergence of serotype 8, and to a lesser extent by serotypes 9N, 12F and 6C (Fig. 2). Serotype 8 was the main serotype in adult IPD in 2016–2018, and its incidence increased from 1.5 per 100,000 in 2009–2011 to 3.7 per 100,000 in 2016–2018. The incidence of emerging serotype 22F did not increase further after the switch to PCV10, and was the fourth most prevalent serotype in IPD in 2016–2018.

3.2. Clinical follow-up (June 2004 to May 2016)

3.2.1. Study population

Both clinical and serotype data were available from 7254 IPD patients of whom 1215 were diagnosed in the pre-PCV period (June 2004–May 2006), 1732 in the post-PCV7 period (June 2008–May 2011) and 1776 in the post-PCV10 period (June 2013–May 2016). The mean patient age increased over the three study periods (60 years (SD 24.1) pre-PCV; 63 years (SD 21.0) post-PCV7; 65 years (SD 18.5) post-PCV10: $p < 0.001$). The percentage of patients with a non-immunocompromising comorbidity was higher in the post-PCV10 period compared with the other two study periods ($p < 0.001$), but this was no longer statistically significant after adjustment for age (Table 2). There was no difference in the proportion of IPD cases with an immunocompromising condition between study periods ($p = 0.129$).

3.2.2. Clinical syndromes

After the switch to PCV10, the incidence of meningitis decreased by 23% compared to pre-PCV across all ages (RR: 0.77, 95%CI: 0.61–0.96, Table 2) and was most pronounced in children under 5 years (Fig. 3 and Supplementary Table S2); no statistically significant further decline was observed in the post-PCV10 period compared to the post-PCV7 period (RR: 0.91, 95%CI: 0.74–1.13). The incidence of pneumonia with empyema increased significantly after introduction of PCV7, but did not increase further after the switch to PCV10 (RR: 0.86, 95%CI: 0.64–1.15) and stabilised at a higher level, comprising 4.7% of all IPD post-PCV10 (vs. 5.5% post-PCV7 and 2.4% pre-PCV). Post-PCV10, the proportion of PCV10 type empyema declined significantly (from 49.5% post-PCV7 to 27.7% post-PCV10, $p = 0.003$). A shift towards non-PCV13 type empyema was observed, mainly serotype 15A (from 0% to 6.7% (n = 3)), 22F (from 6.9% (n = 2) to 13.3% (n = 6)) and 8 (from 44.8% (n = 13) to 51.1% (n = 23)).

3.2.3. Patient outcomes

The overall CFR was 13.4% in the post-PCV10 period, which was significantly lower than in the pre-PCV period (16.2%, Table 2). The reduction in CFR was most pronounced in 50–64 year olds and persons ≥65 years, the age groups that contribute most to the CFR. The decline in CFR was established after PCV7 introduction and the switch to PCV10 did not affect overall CFR; adjustment for age did not change this. Between 2004 and 2018, serotype 19F had the highest CFR (Fig. 4). There was no difference in the proportion of ICU admissions between the three study periods.

4. Discussion

Since the introduction of PCV in the Dutch national immunisation programme in 2006, the incidence of IPD has declined, particularly among children under 5 years, with 69% reduction, and adults ≥65 years and older, with 19%. After the switch to PCV10

Fig. 1. IPD incidence by age group and serotype group from June 2004 to May 2018.

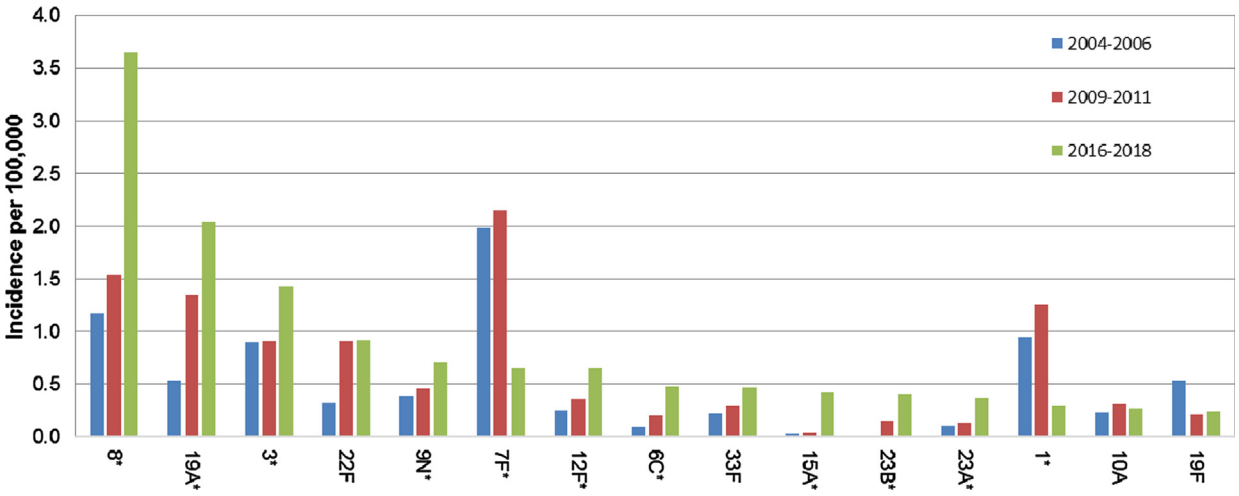

Fig. 2. Incidence before PCV introduction (2004–2006), two years before PCV10 introduction (2009–2011), and the last two years (2016–2018) of the top fifteen serotypes causing IPD in 2016–2018. * Indicates a statistically significant difference ($p < 0.05$) in incidence between 2009–2011 and 2016–2018.

Table 2
Relative risks of patient characteristics, clinical syndrome incidences and outcomes comparing the pre-PCV7, PCV7 and PCV10 period.

	Pre-PCV (2004–2006)	Post-PCV7 (2008–2011)	Post-PCV10 (2013–2016)	Post-PCV10 vs pre-PCV		Post-PCV10 vs post-PCV7	
	n = 1215	n = 1732	n = 1776	RR	95% CI	RR	95% CI
Comorbidity, % (n/N)							
Non-immunocompromising	70.0 (850/1215)	69.9 (1211/1732)	75.4 (1339/1776)	1.08	1.03–1.13	1.08	1.04–1.12
Immunocompromising	20.1 (244/1215)	21.0 (364/1732)	19.1 (339/1776)	0.95	0.82–1.10	0.91	0.80–1.04
Clinical syndrome, /100,000 (N)							
Meningitis	1.68 (137)	1.41 (175)	1.29 (163)	0.77	0.61–0.96	0.91	0.74–1.13
Pneumonia only	10.65 (868)	9.85 (1220)	10.06 (1273)	0.94	0.87–1.03	1.02	0.95–1.11
Pneumonia with empyema	0.36 (29)	0.77 (95)	0.66 (83)	1.84	1.21–2.81	0.86	0.64–1.15
Bact. without focus	1.30 (106)	1.11 (137)	1.23 (156)	0.95	0.74–1.21	1.12	0.89–1.40
Bact. other focus	0.82 (67)	0.81 (100)	0.80 (101)	0.97	0.71–1.32	0.99	0.75–1.30
Patient outcomes, % (n/N)							
ICU admission	21.8 (258/1181)	21.3 (364/1708)	21.9 (389/1776)	1.00	0.87–1.15	1.03	0.91–1.17
Case fatality*	16.2 (194/1201)	11.8 (201/1708)	13.4 (235/1750)	0.83	0.70–0.99	1.14	0.96–1.36
<5 years	5.6 (5/90)	3.6 (2/55)	8.1 (3/37)	1.46	0.37–5.80	2.23	0.39–12.7
5–17 years	4.4 (1/23)	3.1 (1/32)	4.0 (1/25)	0.88	0.06–13.3	1.24	0.98–18.9
18–49 years	4.4 (8/180)	5.1 (14/275)	4.4 (10/227)	0.99	0.40–2.46	0.91	0.41–2.00
50–64 years	12.8 (32/250)	7.7 (33/428)	8.5 (36/424)	0.63	0.40–0.99	1.11	0.71–1.74
≥65 years	22.5 (148/658)	16.5 (151/918)	17.8 (185/1037)	0.75	0.62–0.90	1.10	0.91–1.34
Mortality rate, /100,000 (N)	2.38 (194)	1.62 (201)	1.86 (235)	0.78	0.65–0.94	1.14	0.43–3.08

Abbreviations: Bact., bacteraemia; CI, confidence interval; ICU, intensive care unit; N, number of cases; PCV, pneumococcal conjugate vaccine; RR, relative risk; yr., year.
* Number of missing values/age group (<5,5–17,18–49, 50–64, ≥65 years, respectively): pre-PCV7 (3,–,2,8,11); post-PCV7 (3,–,2,8,11); post-PCV10 (–,–,2,6,18).

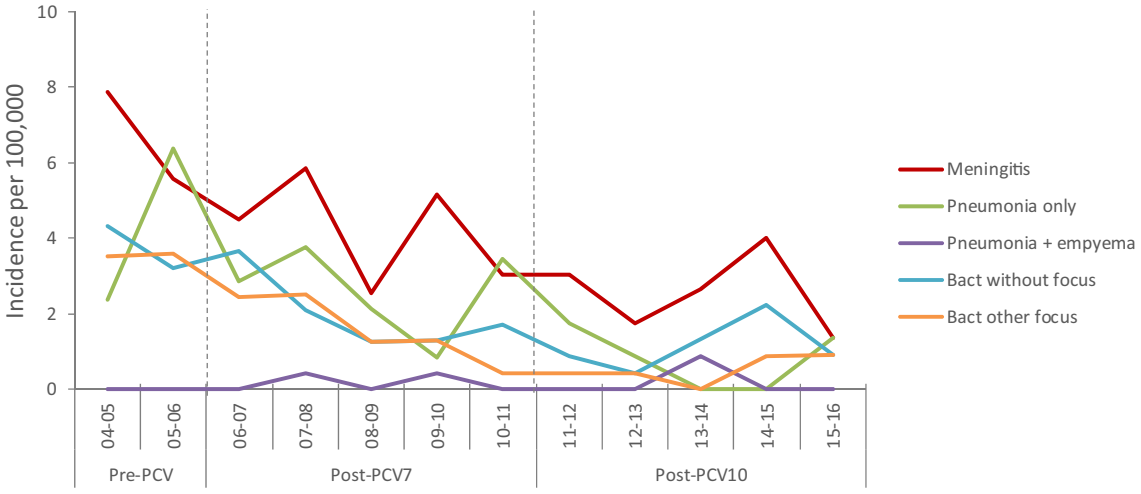

Fig. 3. Incidence of clinical syndromes in children under 5 years (2004–2016).

in 2011, a further 30% reduction in overall IPD was observed in those under 50 years of age, but no reduction was seen in those aged 50–64 years and ≥65 years. In these older age groups, the ongoing decline in vaccine serotypes was countered by the continuous increase in non-vaccine serotype IPD, that resulted in stabilisation of the overall IPD incidence. Since older adults and the elderly (≥65 years) account for almost 90% of reported IPD cases in the Netherlands, no overall net benefit on IPD incidence across all age groups was observed after the switch from PCV7 to PCV10. As the remaining proportion of vaccine-type IPD in 2016–2018 was only 11% compared with 65% in 2004–2006, this suggests that the maximum impact of PCV10 has almost been achieved. Likewise, while the overall CFR decreased after PCV7 introduction, no further reduction was observed after the switch to PCV10. The incidence of empyema stabilised in the post-PCV10 period, after it had increased in the post-PCV7 period, due to a reduction in PCV10-type empyema.

High-quality surveillance data on impact of PCV10 is limited. A recent review of observational data on the impact of current childhood PCV programmes included data from four countries using PCV10, of which one had no prior PCV7 use (Finland) and two had recently switched from PCV10 to PCV13 (Quebec/Canada and New Zealand); the Netherlands was the only country in this review that used PCV10 after previous PCV7 introduction [14]. Data from Finland showed a 79% reduction in overall IPD incidence in vaccine eligible children; this appears slightly more than the overall 69% reduction in children under 5 years in the Netherlands [15]. Among the elderly, Finnish data showed that while reductions in PCV10 type IPD were seen after PCV10 introduction, a simultaneous large increase in non-PCV10 type IPD incidence was observed, resulting in no net benefit of PCV10 introduction [16].

More data have been published on the impact of PCV13. In England and Wales, a continuous reduction in IPD incidence across all ages was observed in the first three years after the switch from PCV7 to PCV13 in 2010 [10]. However, from 2015, replacement by non-PCV13 serotypes eroded the previous PCV13 benefit and only a small net benefit was retained in 2016–2017, compared with the two-year period before PCV13 introduction (RR: 0.93, 95%CI: 0.89–0.97). It is noteworthy that England and Wales found a slightly larger reduction in IPD incidence in children <5 years

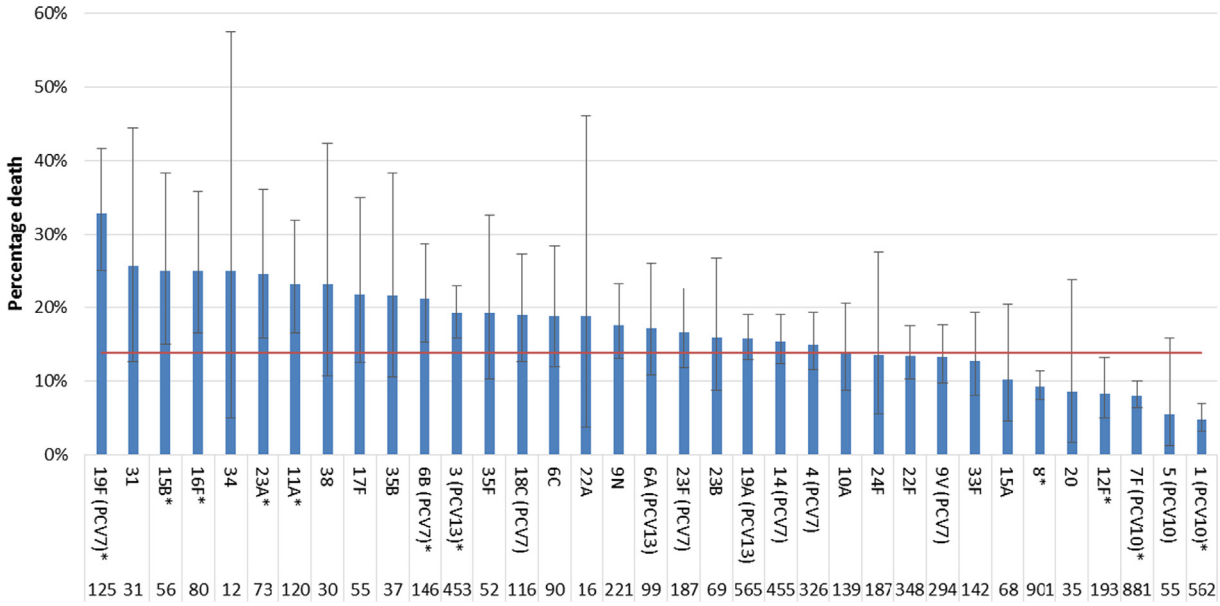

Fig. 4. Serotype specific propensity for death. Serotype specific case-fatality with 95% Confidence intervals (Agresti–Coull method) in all patients. Included are all data from June 2004 to May 2018. All (additional) serotypes included in the 7, 10 and 13-valent pneumococcal conjugate vaccines are shown. From non-vaccine serotypes all serotypes with at least 5 cases and 2 deaths are shown. The horizontal line represents overall case-fatality (14%). * Indicates a statistically significant difference (p-value <0.05) between serotype specific case-fatality versus all other serotypes tested with Fisher's exact test. The numbers represent the total number of isolates per serotype. Abbreviations: PCV, pneumococcal conjugate vaccine.

(36–48%) upon PCV13 introduction compared with the 32% reduction in the Netherlands after the switch to PCV10, likely due to reduction of the additional serotypes covered by PCV13, especially 19A. In Dutch adults between 50 and 64 years, the reduction in PCV10-type IPD incidence was countered by non-vaccine-type IPD after the switch to PCV10. Similarly, in England and Wales the initial reduction in IPD incidence in 45–64 year olds after the switch to PCV13 was eroded over time due to the increase of non-vaccine serotypes. In the elderly of ≥65 years, both countries observed a slight increase of around 5% in IPD, mainly due to a rise in non-PCV13 serotypes 8, 9N and 12F.

With respect to the serotypes included in PCV13 but not in PCV10, in the Netherlands 19A IPD increased slightly after the switch to PCV10, and is one of the main serotypes causing IPD across all age groups, whereas in England and Wales an initial decline in 19A IPD was observed after PCV13 introduction. IPD due to serotype 6A had already declined substantially in both countries after PCV7 introduction. Serotype 3 IPD increased in both the Netherlands and England and Wales, likely due to secular trends, despite the fact that serotype 3 is included in PCV13. Although similar impact on overall IPD has been observed after the switch to PCV10 in the Netherlands, and to PCV13 in England and Wales (compared with their respective periods before *PCV7* introduction), England and Wales still have a net benefit of around 40% across all age groups, compared to a statistically non-significant 6% in the Netherlands. This seems to be mainly due to the much larger impact of childhood pneumococcal vaccination in 45–64 year olds in England and Wales, and the greater contribution of this age group to the overall IPD burden in England and Wales, compared with the Netherlands.

A recent meta-analysis including European data assessed the impact of childhood vaccination on IPD incidence in people aged 65 years and older, comparing 2015 data with 2009 data. This study included six sites with universal PCV13 vaccination for infants, including England and Wales, and four sites with universal PCV10 (+/− PCV13) vaccination, including the Netherlands [16]. The study showed a decline in all-type IPD incidence of 14% (−4 to 30%) in PCV13 sites and 1% (−21 to 18%) in PCV10 sites. A major difference was seen between the PCV13 sites and PCV10 sites with respect to serotype 19A incidence, with decreasing trends in PCV13 sites and increasing trends in PCV10 sites. Similar to what was observed in England and Wales, the decrease of serotype 19A incidence in the PCV13 sites halted in 2015.

Comparison of surveillance data between countries remains difficult because of differences in health care practices, pre-vaccine epidemiology and vaccination policies. Interestingly, in Sweden, different counties switched either to PCV10 or PCV13 after PCV7 and therefore the impact of both vaccines could be compared within the country. The study found, as expected, a differential impact of PCV10 and PCV13 on serotype 19A IPD, with an increase of 19A IPD in PCV10 counties. However, the study did not find a difference in the overall impact on IPD incidence and rate of non-vaccine serotype IPD replacement between PCV10 and PCV13 [17]. Recent data from Belgium also showed the differential impact of PCV10 and PCV13 on serotype 19A IPD, as an increase in 19A IPD was observed in children ≤2 years of age following the switch from PCV13 to PCV10 in 2015–2016 [18]. Longer-term data on 19A and overall IPD from Belgium, and other countries that switched from PCV13 to PCV10, are needed to confirm this.

The decrease in CFR after PCV7 introduction from 16% to 12% in the Netherlands did not continue after the introduction of PCV10, due to the higher burden of IPD from serotypes associated with higher fatality such as 19A, 9N and 3, and a reduction of PCV10 serotypes 1 and 7F which cause less mortality. In England and Wales, the CFR in children under 5 years was 5.1% in the six years after PCV13 introduction (2010–2016) [19] vs. 4.4% after PCV7 introduction (2006–2010) [20]. At the same time, the prevalence of comorbidity among children with IPD increased, indicating that a shift in patient characteristics might influence the CFR. In the Netherlands, we observed a rise in both age and the proportion of cases with non-immunocompromising comorbidities, mainly in the elderly, but adjustment for these variables did not change the association between time period and CFR. To the best of our knowledge, no other reports on changes in CFR in adults in relation to PCV10 or PCV13 introduction have been published.

As stated by the recently published WHO position paper [21], there is at present insufficient evidence of a difference in the net impact of the two vaccines on overall IPD burden. The benefit of vaccination for the elderly with PCV13 depends on the serotype distribution of IPD in this age group, but in many countries, PCV13 likely has a limited effect, because of the large indirect effects of infant PCV10 and PCV13 vaccination on vaccine-type IPD in the elderly. On the other hand, the potential additional benefit of PPV23 vaccination has increased, because of the expanded PPV23 coverage of emerging serotypes like 8, 9N and 12F. A recent cost-effectiveness analysis in the Netherlands showed that PPV23 was superior to PCV13 in adults 60 years and older in all investigated scenarios, despite the relatively moderate effectiveness and the limited duration of protection of PPV23 [22]. Routine vaccination with PPV23 every five years, among older adults 60–75 years has been advised by the Dutch Health Council as of February 2018 [23], and is planned for implementation at the end of 2019.

Higher-valent vaccines, including 15-valent and 20-valent conjugate vaccines, are currently being evaluated for safety and immunogenicity in phase 3 trials [24,25]. Another current issue is the development of whole cell and recombinant protein vaccines, which could offer serotype-independent protection, although these vaccines are still years from clinical implementation.

The main strength of this study is that we obtained data from a sentinel surveillance system that has not changed its methods over time. This has allowed us to collect reliable clinical and serotype data across vaccination periods. Even though the CAPiTA study, in which Dutch persons of ≥65 years were vaccinated with PCV13, coincided with our post-PCV7 period, its influence on our results is expected to be negligible: despite its large sample size of 85,000 participants, this only accounts for 3% of all persons of ≥65 years in the Netherlands [26].

Our study had an observational design. Therefore, factors other than vaccination might have affected our results. Even though we adjusted for age and/or comorbidities when applicable, unknown confounders might still have been present, so no causal relationship between PCV and observed outcomes can be established. Despite our strong sentinel surveillance system with no change in coverage over time, the system only covers 25% of the Dutch population which may affect the generalizability of the results. Also, shifts in long-term secular pneumococcal serotype trends may have influenced the results.

5. Conclusions

Although we still observe a net benefit of introduction of PCV on IPD incidence in children and elderly, and on the CFR of IPD in the Netherlands, IPD incidence could rebound in the near future as vaccines have nearly reached their maximum effect, serotype replacement is ongoing, and the population is aging. New vaccines, either with broader serotype coverage or focused on the pneumococcus as a whole, might be needed to reduce the burden of IPD in the future. Ongoing monitoring of IPD serotype distribution and clinical outcomes is warranted, to evaluate existing vaccination policies and to inform new vaccination policies.

CRediT authorship contribution statement

Stefan M.T. Vestjens: Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing - original draft. **Elisabeth A.M. Sanders**: Conceptualization, Formal analysis, Funding acquisition, Investigation, Writing - review & editing. **Bart J. Vlaminckx**: Conceptualization, Writing - review & editing. **Hester E. de Melker**: Conceptualization, Writing - review & editing. **Arie van der Ende**: Conceptualization, data curation, Project administration, Resources, Writing - review & editing. **Mirjam J. Knol**: Conceptualization, data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Visualization, Writing - original draft.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

EAMS has received grant support from Pfizer and GlaxoSmithKline for research on vaccine studies (fees paid to University Medical Center Utrecht before 2015). AE has received a grant from Pfizer for research on pneumococcal infections (Investigator Initiated project: "Epidemiology of invasive pneumococcal disease" IIR WI173197) and participated in Advisory Boards of Pfizer and does consultancy activities for GlaxoSmithKline (fees paid to Amsterdam University Medical Center). All other authors report no potential conflicts.

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Appendix A. Supplementary material

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