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Effect of childhood pneumococcal conjugate vaccination on invasive disease in older adults of 10 European countries: implications for adult vaccination

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ABSTRACT

Background Pneumococcal conjugate vaccines (PCVs) have the potential to prevent pneumococcal disease through direct and indirect protection. This multicentre European study estimated the indirect effects of 5-year childhood PCV10 and/or PCV13 programmes on invasive pneumococcal disease (IPD) in older adults across 13 sites in 10 European countries, to support decision-making on pneumococcal vaccination policies.

Methods For each site we calculated IPD incidence rate ratios (IRR) in people aged ≥65 years by serotype for each PCV10/13 year (2011–2015) compared with 2009 (pre-PCV10/13). We calculated pooled IRR and 95% CI using random-effects meta-analysis and PCV10/13 effect as (1 − IRR)*100.

Results After five PCV10/13 years, the incidence of IPD caused by all types, PCV7 and additional PCV13 serotypes declined 9% (95% CI −4% to 19%), 77% (95% CI 67% to 84%) and 38% (95% CI 19% to 53%), respectively, while the incidence of non-PCV13 serotypes increased 63% (95% CI 39% to 91%). The incidence of serotypes included in PCV13 and not in PCV10 decreased 37% (95% CI 22% to 50%) in six PCV13 sites and increased by 50% (95% CI −8% to 146%) in the four sites using PCV10 (alone or with PCV13). In 2015, PCV13 serotypes represented 20–29% and 32–53% of IPD cases in PCV13 and PCV10 sites, respectively.

Conclusion Overall IPD incidence in older adults decreased moderately after five childhood PCV10/13 years in 13 European sites. Large declines in PCV10/13 serotype IPD, due to the indirect effect of childhood vaccination, were countered by increases in non-PCV13 IPD, but these declines varied according to the childhood vaccine used. Decision-making on pneumococcal vaccination for older adults must consider the indirect effects of childhood PCV programmes. Sustained monitoring of IPD epidemiology is imperative.

Key messages

What is the key question?

- This study assesses the indirect effect of 5 years of childhood PCV10 and/or PCV13 programmes on invasive pneumococcal disease (IPD) in older adults across 10 European countries, using the same methodology.

What is the bottom line?

- Previous studies in single countries and using different methodologies showed diverging results in terms of overall benefit (IPD incidence) and serotype replacement disease.

Why read on?

- Our study reveals that the effect on IPD in older adults differs according to the PCV used in the childhood programme and highlights the continuing rise in non-PCV13 serotypes; these findings are important when deciding on pneumococcal vaccination policy for older adults.

INTRODUCTION

Streptococcus pneumoniae is associated with significant morbidity and mortality in older adults. The most severe form, invasive pneumococcal disease (IPD), includes bacteraemic pneumonia, meningitis and septicaemia.[1 2] In recent European studies the annual incidence of IPD in persons aged ≥65 years ranged from 10 to 70 per 100 000.[1–5] Pneumococcal conjugate vaccines covering 10 (PCV10) and 13 (PCV13) serotypes (table 1) have progressively replaced the 7-valent vaccine (PCV7) in the childhood vaccination schedule of most European countries during 2010 or 2011. PCV vaccination policies are heterogeneous between countries. In 2014, among 17 Western European countries, eight used PCV13 only, four used PCV10 only and five used both vaccines in the childhood vaccination programme.[6] PCV13 has also been approved in

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Table 1 Serotype categories causing invasive pneumococcal disease according to the serotype content of vaccines

Category of serotypes	Serotypes
PCV7	4, 6B, 9V, 14, 18C, 19F and 23F
PCV13non7 (in PCV13 and not in PCV7)	1, 3, 5, 6A 7F and 19A
PCV10non7 (in PCV10 and not in PCV7)	1, 5 and 7F
PCV13non10 (in PCV13 and not in PCV10)	3, 6A and 19A
Non-PCV13 (any not in PCV13)	Any serotype not in PCV13
PPV23non13 (in PPV23 and not in PCV13)	2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F and 33F
Non-vaccine (not in PCV13 nor in PPV23)	Any serotype not in PCV13 and not in PPV23

adults for the prevention of IPD since 2011 and in 2015 the indication was extended to pneumococcal pneumonia.[7]

Childhood PCV vaccination may have an indirect effect on unvaccinated population groups, especially on older adults (in whom the incidence of IPD is very high), through a reduction in carriage of vaccine serotypes in vaccinated children, with subsequent reduction in circulation and transmission across all age groups. However, this indirect effect is also responsible for an increase in non-PCV serotypes, called serotype replacement. Indeed, after the introduction of PCV7, the decline in PCV7 serotype IPD was partly countered by replacement with non-PCV7 serotypes. A few countries have also recently reported an indirect effect in adults aged ≥65 years 3–4 years after PCV10/13 replaced PCV7 in the childhood vaccination programme.[8–12] The decrease in overall IPD incidence after each PCV introduction is generally limited (<25%) because of serotype replacement disease, but its extent is unclear because of large confidence intervals.[8–12]

Some countries with established childhood PCV10/13 programmes are currently considering whether to introduce PCV13 vaccination in elderly people. A key question, therefore, is what additional value such a programme might offer over the indirect effect of a childhood PCV10/13 programme. In older adults, the polysaccharide 23-valent vaccine (PPV23) aims to protect against 12 PCV13 serotypes and 11 additional non-PCV13 serotypes, but its effectiveness against pneumococcal disease in this age group remains controversial.[13 14]

SpIDnet and I-MOVE+ are complementary European multicentre surveillance projects funded by the European Centre for Disease Prevention and Control (ECDC) and the European Commission since 2012 and 2015, respectively, to monitor the impact and effectiveness of PCV programmes in Europe. In 2015, SpIDnet and I-MOVE+ collected IPD data in adults from 13 sites across 10 countries: the Czech Republic, Denmark, England and Wales, Finland, France, Ireland, the Netherlands, Norway, Scotland, Sweden and the Madrid, Catalonia and Navarre regions of Spain. PCV7 was introduced in the childhood vaccination schedule (2001–2009) across all sites except Finland and replaced in 2010–2011 with either universal PCV13 (six sites), universal PCV10 (two sites) or both PCV10 and PCV13 (five sites, two with universal and three with non-universal PCV10/13), without catch-up vaccination. At the time of this study (2016), none of the sites routinely recommended PCV13 for all older adults. Nine sites recommended PPV23 for this age group; PPV23 uptake varied between 15% and 70% (table 2). Five sites recommended PCV13 for at-risk groups, together with PPV23.

Table 2 Vaccination programme, population size, proportion of invasive pneumococcal disease (IPD) cases serotyped and number of IPD cases per year among older adults aged ≥65 years by site: SpIDnet/I-MOVE+ multicentre study

	Vaccine used (uptake) in 2015		Population aged ≥65 years	% typed cases††	Adjusted number of cases* per year						
Sites	In infants	In elderly (any)	2015	2015	2009	2010	2011	2012	2013	2014	2015
CZ	U, PCV10/PCV13 (71%)†	PPV23 (NA)	1 932 412	93%	151	139	134	142	183	157	191
DK	U, PCV13 (94%)	PPV23 (11%), PCV13 (3%)	1 072 422	94%	569	539	540	544	475	483	560
EW	U, PCV13 (94%)	PPV23 (70%)	11 000 000	96%	2380	2378	2158	2189	2138	2187	2739
FI	U, PCV10 (94%)	Risk groups (PPV23 <5%)	1 123 103	99%	295	304	297	342	319	355	427
FR	U, PCV13 (94%)	Risk groups (PPV23 8%)	9 209 601	NA‡	2539	2410	2396	2258	1881	1640	1820
IE	U, PCV13 (93%)	PPV23 (36%)§; PCV13 risk groups¶	606 011	88%	156	147	160	177	171	168	189
NL	U, PCV10 (94%)	Risk groups	751 921	100%	331	303	334	360	377	313	402
NO	U, PCV13 (93%)	PPV23 (15%)	834 302	99%	381	390	381	327	307	311	312
SC	U, PCV13 (97%)	PPV23 (69%)	982 998	89%	219	255	218	238	285	221	313
SE	U, PCV10/PCV13 (97%)†	Risk groups	1 912 884	95%	866	819	743	832	789	747	787
CAT	PCV10/PCV13 (78%)	PPV23 (60%)	1 361 617	90%	490	456	344	413	451	388	449
MAD	PCV10/PCV13 (77%)§	PPV23 (60%)	1 079 912	91%	192	174	184	190	183	238	254
NAV	(PCV10) PCV13 (81%)**	PPV23 (57%)	121 236	90%	30	22	33	34	26	25	30
All	NR	NR	31 988 419	95%	8599	8336	7922	8046	7585	7233	8473

*Adjusted for the sensitivity of the surveillance system.
†PCV10 and PCV13 are used in similar proportions in those sites.
‡Not computed as two different datasets are used (no case reconciliation).
§2013.
¶ Starting August 2015.
**PCV13 was used almost exclusively as the PCV10 uptake in children aged <2 years has been <1% since 2012.
††The number of serotyped cases divided by all reported cases in that site in 2015.
CAT, Catalonia; CZ, Czech Republic; DK, Denmark; EW, England & Wales; FI, Finland; FR, France; IE, Ireland; MAD, Madrid; NAV, Navarra; NL, the Netherlands; NOR, Norway; NA, not available; NR, not relevant; SC, Scotland; SE, Sweden; U, universal programme.

We estimated the indirect effect of the childhood PCV10/13 programme on IPD in adults aged ≥65 years (herein referred to as 'older adults') across these 13 sites during the first 5 years of PCV10/13 use, in order to support decision-making on the pneumococcal vaccine policy for older adults across Europe.

METHODS

IPD surveillance systems and data sources

The 13 study sites conduct population-based IPD surveillance, with laboratory confirmation and serotyping of invasive pneumococcal isolates from cases residing in the catchment area. In 2015, reporting of IPD cases was mandatory in 11 sites and voluntary in two sites. IPD cases were defined according to the 2012 ECDC case definition.[15] Aggregated data were collected from each surveillance site by calendar year and serotypes. All cases identified through surveillance were included in the analysis.

The reference laboratories at the respective surveillance sites used capsular reaction with specific antisera (Quellung reaction) or PCR for serotyping. Serotypes 6A and 6C were differentiated by PCR, Quellung or latex agglutination with specific antisera at all sites. The national reference laboratories participated in the external quality schemes organised by the ECDC during 2010–2014. Serotypes causing IPD were classified into categories according to the serotype content of vaccines (see table 1).

Analysis of data

We measured the indirect effect of the childhood PCV10/13 vaccination programme in older adults by comparing the incidence rate in this age group within a population with an established childhood PCV10/13 programme with the incidence rate in the same age group in the pre-PCV10/13 period.[16 17] The pre-vaccine period represents the reference population (without a routine PCV10/13 programme) at each site.

For each site we accounted for missing serotype data by assuming the same serotype distribution in cases with and without serotype information, by calendar year. For three sites that reported a change in surveillance sensitivity over the surveillance period, we adjusted the number of reported cases to the sensitivity for each period, as described elsewhere.[18–20] We computed annual incidence rates per site and serotype by dividing the numbers of cases adjusted for missing serotyping data and under-reporting by the respective source population.

For each site we thus compared the incidence of IPD in people aged ≥65 years before and after the introduction of childhood PCV10/13. We calculated site-specific incidence rate ratios (IRR) between 2009 and each of the PCV10/13 years (2011–2015) by serotype category. As data availability and the number of years after PCV7 introduction varied across sites in the pre-PCV10/13 period, we selected 2009 as the pre-vaccination period because it was the last pre-PCV10/13 year common to all sites. We performed sensitivity analysis using the average incidence during the PCV7 years as the pre-PCV10/13 period (and 2005–2008 for Finland). We considered 2010 as a transition year because PCV13/10 became available shortly before or during that year.

We computed pooled IRR and 95% CI by serotype category and year using random effects meta-analysis, as we assumed that the true indirect effect could vary across sites.[21] We also performed pooled analyses stratified by the childhood vaccine used. We assessed statistical heterogeneity by estimating the between-study variance using tau-squared (τ^2), which is less dependent on the number of sites and the precision of site estimates than other heterogeneity measures.[22] Heterogeneity between studies was considered to be low if τ^2 <0.2, fairly reasonable for τ^2 between 0.2 and 0.5 and fairly high for τ^2 >0.5 and <1.0.[23] The indirect effect of PCV on IPD in older adults was expressed as the percentage change in incidence ((1 − IRR)*100). Statistical analyses were performed using STATA 12.0 (StataCorp, Texas, USA).

RESULTS

In 2015 the 13 sites covered around 32 million adults aged ≥65 years (table 2). PCV uptake in the infant programme exceeded 93% in 9/10 sites with universal vaccination, and ranged between 77% and 81% in the three sites with non-universal vaccination. A total of 56 194 IPD cases were reported among people aged ≥65 years during 2009–2015. Overall, serotyping was performed for 92% of the invasive pneumococcal isolates, excluding France where the incidence and serotype distribution are reported through two different systems without case reconciliation as described elsewhere,[19] and the serotyping rate cannot be calculated. The serotyping rate ranged from 91% to 95% annually (for all sites) and from 88% to 100% across the sites (for all years).

Change in IPD incidence

In the pre-PCV10/13 period the overall IPD incidence rates varied by site (figure 1), with higher rates in the Nordic countries and the Netherlands. Based on point estimates, IPD incidence rates decreased from 2009 to 2014 in 11/13 sites and increased from 2014 to 2015 in 12/13 sites (95% CI around IRR including 1 in 7/12 sites), exceeding the 2009 rates in 4/13 sites (95% CI around IRR including 1 in two sites, figure 2A). Pooled analysis estimated an overall decline of 9% (95% CI −4% to 19%) in IPD incidence in 2015 compared with 2009 (pre-PCV10/13 period, figure 3A, table 3).

The point estimate incidence of PCV7 serotype IPD declined across all sites except one (figure 2B). The pooled analysis indicated a progressive decline in incidence reaching 77% (95% CI 67% to 84%) in 2015 compared with 2009 (figure 3A, table 3). PCV13non7 serotype IPD incidence declined in 11/13 sites over the same period, with a pooled estimate decline of 38% (95% CI 19% to 53%) in 2015 (figure 3A, table 3). PCV10non7 serotype IPD incidence decreased across all sites (figure 2C), reaching 73% (95% CI 59% to –82%) decline by 2015 in the pooled analysis (figure 3B, table 3). Changes in PCV13non10 serotype IPD incidence varied by site; site-specific IRR ranged between 0.4 and 2.9 in 2015 compared with 2009 (figure 2D). The pooled analysis showed a decline in PCV13non10 serotype IPD incidence up to 2014 followed by an increase in 2015 (figure 3B) based on point estimates, although with overlapping 95% CI around the IRR. The pooled IRR for serotype 3 IPD fluctuated around 1 during the PCV10/13 period (figure 3B, table 3). The incidence of IPD due to serotype 19A declined over time but with wide confidence intervals (figure 3B, table 3). When the average PCV7 period was used as the pre-vaccine period instead of the 2009 year, similar patterns were observed with a decline of 11% (95% CI 0% to 21%) in overall IPD, 83% (95% CI 73% to 89%) in PCV7 serotypes and 33% (95% CI 11% to 50%) in PCV13non7 serotype IPD incidence by 2015.

The point estimate incidence of non-PCV13 serotype IPD increased in 12/13 sites over the PCV10/13 period (figure 2E), with a pooled increase of 63% (95% CI 39% to 92%) in 2015 (figure 3A). Pooled IRR was similar for the 11 non-PCV13

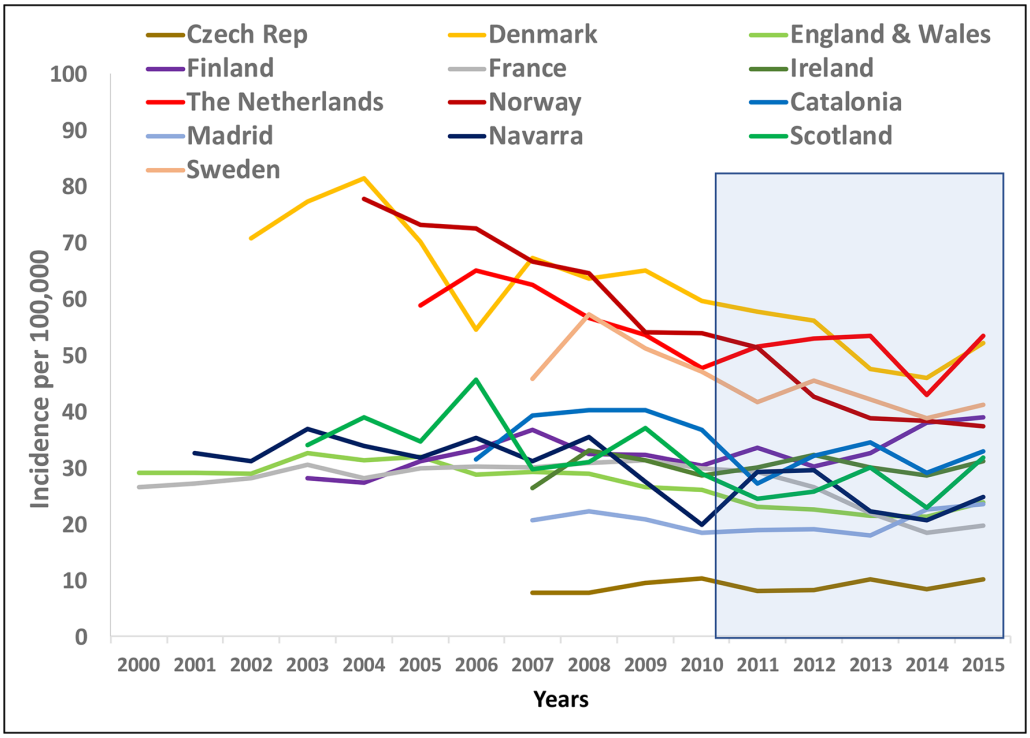


Figure 1 Overall incidence of invasive pneumococcal disease per site and years in persons aged ≥65 years over the period 2000–2015: SpIDnet/I-MOVE+ multicentre study.

serotypes included in PPV23 (PPV23non13) (IRR 1.53, 1.39–1.68) and the non-vaccine serotypes (1.78, 1.41–2.24; figure 3C).

Changes in incidence according to childhood vaccination

We compared pooled IRR for six sites with universal PCV13 with those of four sites with universal PCV10, used exclusively (two sites) or in similar proportion with PCV13 (two sites) (figure 4). From 2009 to 2015, the overall IPD incidence declined by 14% in PCV13 sites (95% CI −4% to 30%) and by 1% (−21% to 18%) in PCV10 sites. IPD due to PCV7 and PCV10non7 serotypes decreased in both groups, by 85% (95% CI 82% to 88%) and 77% (95% CI 60% to 86%) in PCV13 sites and by 78% (95% CI 57% to 89%) and 53% (95% CI 24% to 71%) in the sites using PCV10, respectively. IPD due to PCV13non10 serotypes decreased by 37% (95% CI 22% to 49%) in PCV13 sites and increased by 50% (95% CI −8% to 146%) in the sites using PCV10. Overall, PCV13non7 serotype IPD declined by 51% (95% CI 39% to 61%) in PCV13 sites and increased by 19% (95% CI −26% to 90%) in PCV10 sites, although with overlapping 95% CI. The incidence of IPD due to serotype 19A decreased by 47% (95% CI 38% to 61%) in PCV13 sites and increased by 174% (95% CI 51% to 399%) in PCV10 sites, with the largest increases seen in 2015. The incidence of serotype 3 IPD fluctuated in both groups, but decreased in the first 4 years among PCV13 sites and tended to increase in PCV10 sites. Non-PCV13 type IPD showed similar trends in both groups.

Serotype distribution among IPD cases in older adults during 2015

In 2015, PCV7 serotypes represented <20% of all IPD cases in older adults at each site (figure 5), with a range of 2–4% in PCV13 sites, 6–16% in sites using PCV10 and 10–19% in the four sites with limited PCV7 vaccination (none or median uptake ≤60%) before the introduction of PCV10/13 (i.e. Catalunya, Navarra, Czech Republic and Finland). Note that Madrid had universal PCV7 vaccination between 2007 and 2010 (vaccine uptake >90%), replaced by universal PCV13 vaccination up to May 2012. PCV10non7 serotypes were responsible for ≤5% of IPD cases in all sites except one. PCV13non10 serotypes caused 11–23% of IPD cases in PCV13 sites and 20–36% in PCV10 sites. Altogether, PCV13 serotypes represented 20–29% of IPD cases in PCV13 sites and 32–53% in sites using PCV10. The PPV23non13 serotypes were responsible for 37–54% and 22–46% of IPD cases in PCV13 and PCV10 sites, respectively.

Heterogeneity testing

Based on τ^2, heterogeneity between studies was low or fairly reasonable in all pooled analyses ($\tau^2<0.5$), except for serotype 19A across all sites ($\tau^2=0.5$ in 2015). Heterogeneity was low ($\tau^2<0.2$) in 90% of analyses by vaccine policy and fairly reasonable ($\tau^2=0.2$–0.5) in the remaining 10%.

DISCUSSION

Our pooled analysis of 13 sites from 10 European countries identified a large indirect effect of childhood PCV programmes on IPD among older adults, with IPD caused by PCV7 and PCV10 serotypes declining by more than 70% after five PCV10/13 years compared with the pre-PCV10/13 period. The three serotypes included in PCV13 and not in PCV10 declined moderately (20%), but the trends differed by site according to whether the childhood vaccination programme included PCV10 or PCV13 in individual sites. The incidence of IPD due to non-PCV13 serotypes increased by 63%, restricting the overall changes in IPD incidence to a 9% decline, although with wide confidence intervals, after 5 years of the childhood PCV10/13 programme.

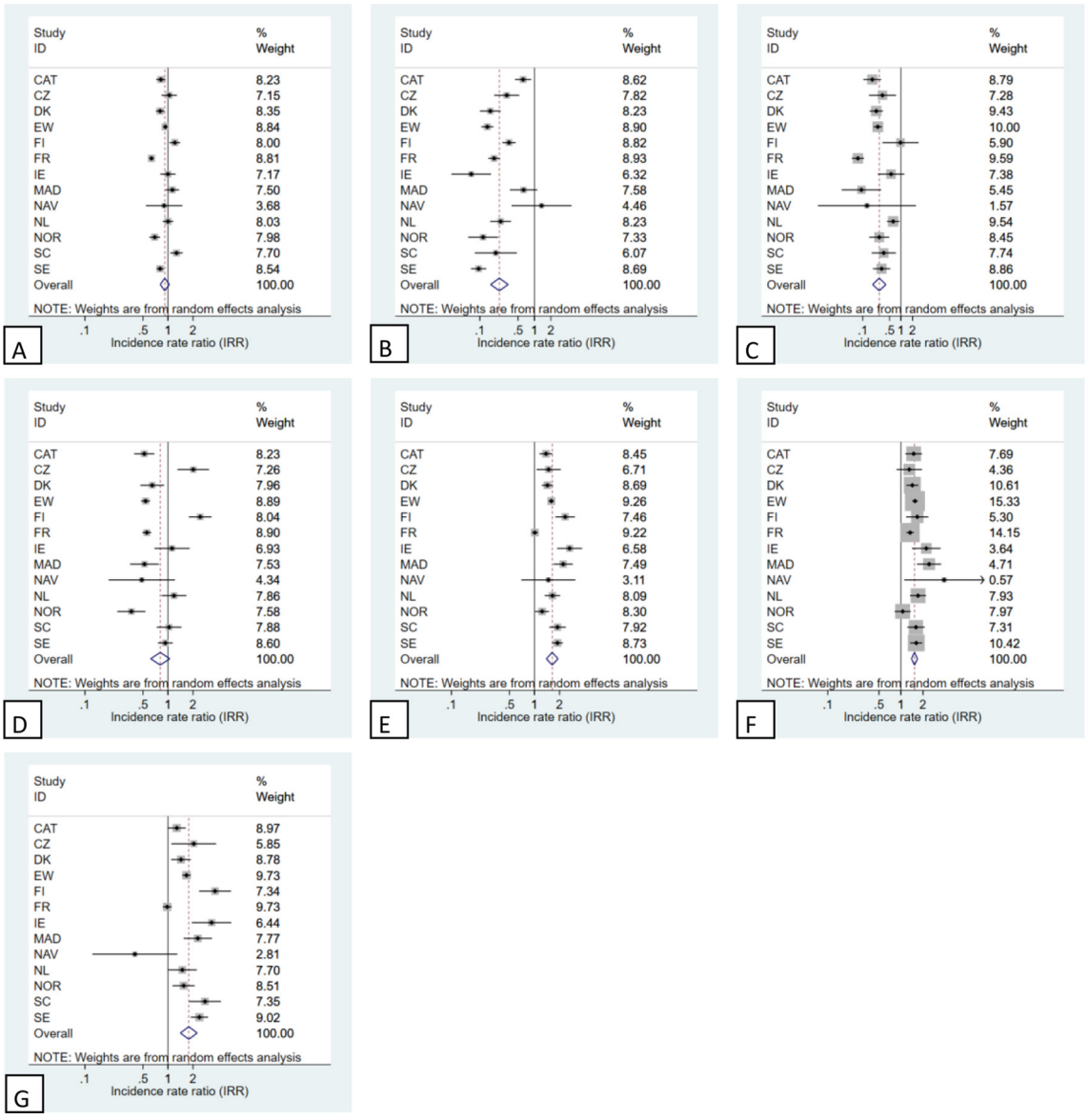


Figure 2 Site incidence rate ratio by serotype category in 2015 compared with 2009: SpIDnet/I-MOVE+ multicentre study. (A) All. (B) PCV7. (C) Included in PCV10 and not in PCV7 (1, 5 and 7F). (D) Included in PCV13 and not in PCV10 (3, 6A and 19A). (E) Non-PCV13. (F) PPV23 non-PCV13. (G) Non-vaccine.

The year-on-year increase in the incidence of non-PCV13 serotypes during the five PCV10/13 years, suggesting serotype replacement in disease, is consistent with recent European reports from other sites during at least four PCV10/13 years and counters the marked declines in vaccine serotype IPD incidence, thereby restricting the overall benefits of the childhood programme on IPD in older adults. In Italy and Germany the incidence or number of reported cases in adults aged ≥65 years tended to increase over the PCV13 period.[24 25] In contrast, in the USA the incidence of non-PCV13 IPD did not increase in older adults after 3 years of the childhood PCV13 programme.[12] Differences in surveillance methodologies, case definitions and clinical practices, as noted since the PCV7 era, along with the shorter surveillance interval in the US study may at least partly explain this difference.[26 27]

The incidence of PCV7 serotype IPD declined substantially. By 2015 these serotypes represented <5% of IPD cases among the older adults in sites where universal PCV13 replaced PCV7 vaccination. In countries with no or limited PCV7 use prior to PCV13 introduction, however, PCV7 serotypes accounted for 10–19% of IPD cases among the older adults in 2015.

We identified important differences in indirect effects according to the PCV used in the childhood programme. After 5 years the point estimate decline in overall IPD among older adults was greater in the six sites with universal PCV13 vaccination compared with the four sites with universal PCV10, used exclusively or in equal proportions with PCV13, although with wide confidence intervals. This difference was partly due to PCV13non10 serotypes, which decreased by 37% in PCV13 sites compared with a 50% increase (with wide confidence intervals) in sites using PCV10. This was driven primarily by diverging trends in the incidence of serotype 19A IPD and could be expected as PCV10 does not contain serotype 19A. IPD incidence due to this serotype also increased rapidly in countries with established PCV7 programmes prior to PCV13 implementation. Although a decline in serotype 19A IPD incidence has been observed in vaccinated children with PCV10,[28 29] potentially through cross-protection from antibodies against serotype

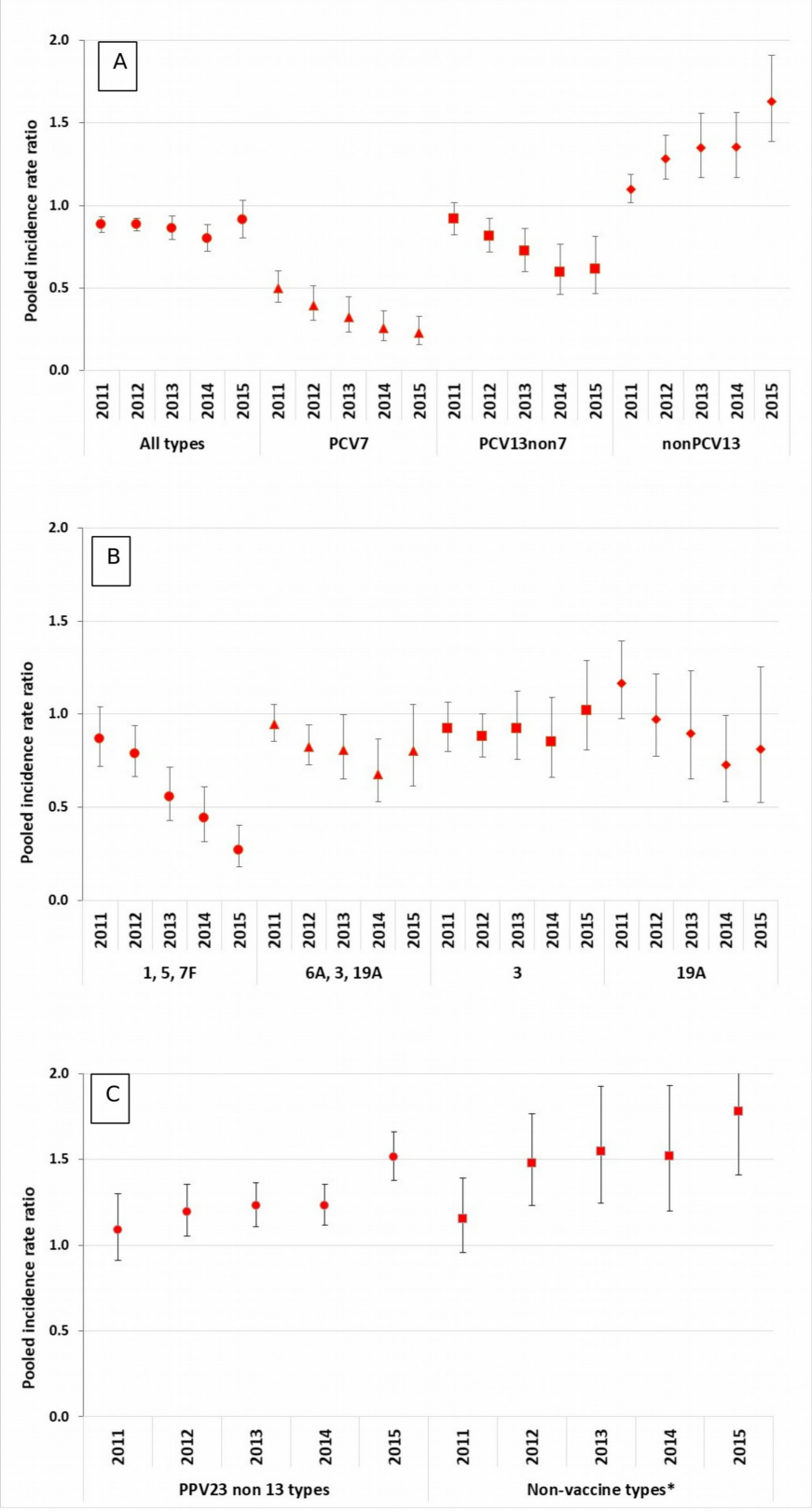


Figure 3 Pooled incidence rate ratio per serotype group over the PCV10/13 years (2011–2015) compared with 2009: SpIDnet/I-MOVE+ multicentre study.

19F, this may not be sufficient to offer indirect (herd) protection for serotype 19A IPD among older unvaccinated individuals.[30] Similar differences were observed in Sweden between counties vaccinating with PCV10 and those vaccinating with PCV13.[5] For serotype 3, the pooled IRR was <1 in PCV13 sites and >1 in PCV10 in 2012–2015, but confidence intervals were too large to allow any conclusive interpretation. Although the incidence of serotype 3 IPD declined in PCV13 sites in the first 4 years

Table 3 Incidence rate ratio of invasive pneumococcal disease (IPD) per PCV10/13 year compared with 2009, 13 sites: SpIDnet/I-MOVE+ multicentre study

Serotypes (group)	2011 (year 1)	2012 (year 2)	2013 (year 3)	2014 (year 4)	2015 (year 5)
All types	0.88 (0.84–0.93)	0.88 (0.85–0.92)	0.86 (0.79–0.93)	0.80 (0.72–0.89)	0.91 (0.81–1.03)
PCV7	0.50 (0.42–0.60)	0.40 (0.30–0.51)	0.32 (0.23–0.44)	0.25 (0.18–0.36)	0.23 (0.16–0.33)
PCV13non7*	0.91 (0.82–1.02)	0.81 (0.72–0.92)	0.72 (0.60–0.86)	0.60 (0.46–0.77)	0.62 (0.47–0.81)
PCV10non7†	0.87 (0.72–1.05)	0.79 (0.66–0.94)	0.56 (0.43–0.72)	0.44 (0.32–0.61)	0.27 (0.18–0.41)
PCV13non10‡	0.95 (0.85–1.05)	0.83 (0.73–0.94)	0.81 (0.65–0.99)	0.68 (0.53–0.87)	0.81 (0.62–1.05)
Serotype 3	0.93 (0.80–1.08)	0.90 (0.78–1.06)	0.98 (0.79–1.22)	0.89 (0.69–1.16)	1.03 (0.81–1.31)
Serotype 19A	1.13 (0.95–1.34)	1.06 (0.82–1.37)	0.98 (0.69–1.38)	0.77 (0.56–1.06)	0.87 (0.56–1.06)
NonPCV13	1.10 (1.02–1.19)	1.28 (1.16–1.42)	1.35 (1.17–1.56)	1.35 (1.17–1.57)	1.63 (1.39–1.92)
PPV23 nonPCV13§	1.09 (0.91–1.30)	1.19 (1.05–1.36)	1.23 (1.11–1.37)	1.23 (1.12–1.36)	1.53 (1.39–1.68)
Non-vaccine¶	1.15 (0.96–1.39)	1.47 (1.23–1.75)	1.54 (1.25–1.91)	1.52 (1.20–1.91)	1.78 (1.41–2.24)

*Serotypes 1, 3, 5, 6A, 7F and 19A.
†Serotypes 1, 5 and 7F.
‡Serotypes 3, 6A and 19A.
§Serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F and 33F.
¶Serotypes not in PPV23 and not in PCV13.

after PCV13 introduction, its increase in 2015 is difficult to explain, thus precluding any conclusion about the ability of the childhood PCV13 programmes to generate herd effects against this serotype. The increase in PCV13non10 serotypes in the four PCV10 sites is problematic because serotypes 3 and 19A already rank among the most prevalent causes of invasive and non-invasive pneumococcal disease among older adults.[2 11]

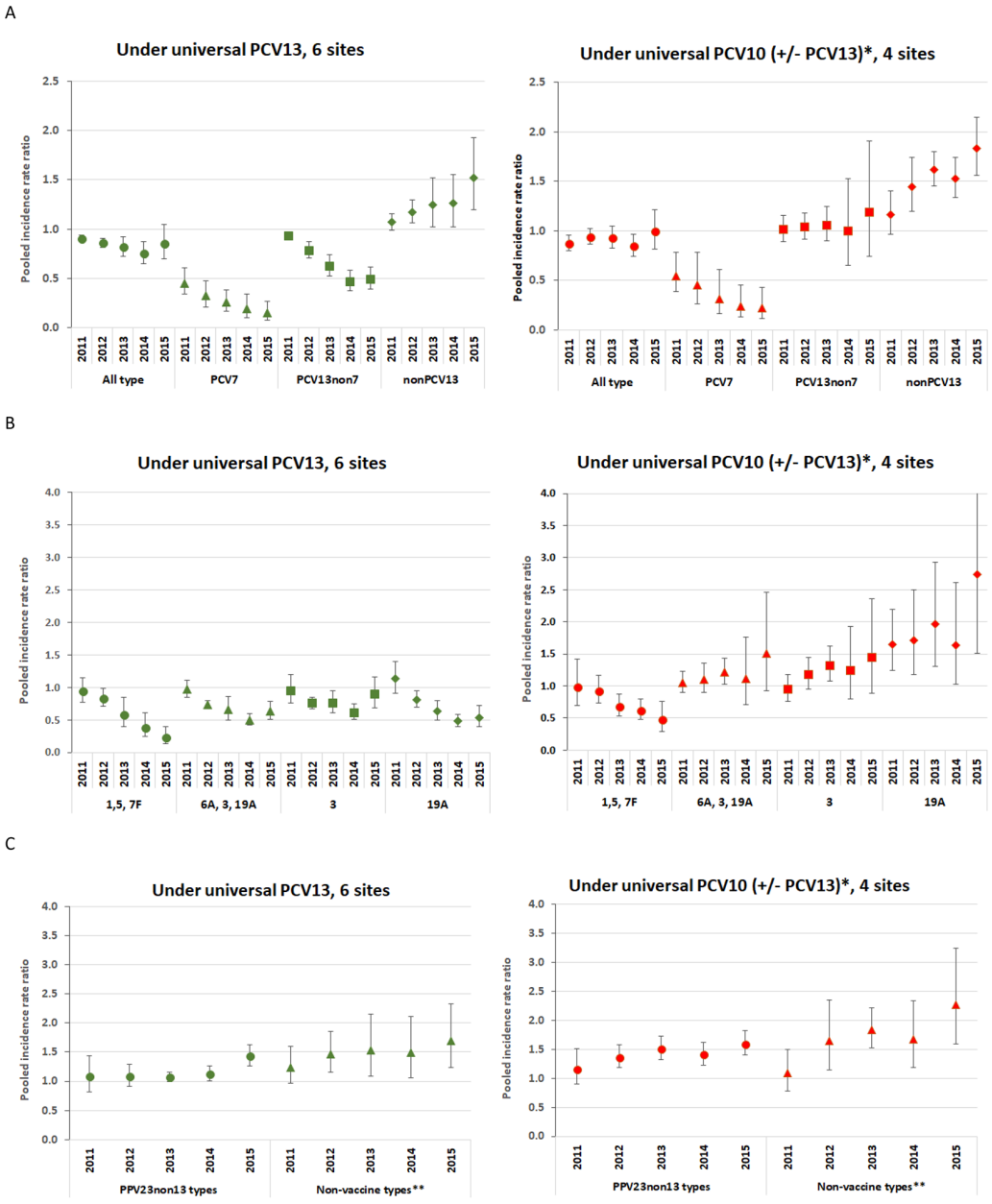
Currently, a major question is whether a PCV13 programme for older adults would present an added value compared with the indirect effect of the childhood PCV10/13 programme. The continuing decline in PCV10/13 serotype IPD in older adults through the indirect benefits of the childhood PCV10/13 programme in this study, as in other European studies,[10 23 25 31 32] is one factor which explains why most European countries do not advise routine PCV13 for older adults. Our study is, however, the first multi-country study to estimate residual PCV13 disease and differing trends depending on the country's childhood PCV policy. In PCV13 sites, PCV13 serotypes represented <30% of all IPD among older adults in 2015 and the incidence of PCV13non7 serotype IPD halved after five PCV13 years. In contrast, in the PCV10 sites, PCV13 serotypes were responsible for one-third to one-half of IPD cases among older adults in 2015 and the incidence of PCV13non7 serotype IPD tended to increase over the five PCV10 years. Although future trends cannot be predicted, our results suggest that, in countries using PCV10 in the childhood schedule, a higher proportion of IPD cases would be targeted by a PCV13 programme for older adults. This group, however, comprises more than 30 1-year age cohorts and such a programme would only offer direct protection to vaccinated older adults.

The incidence of PPV23non13 serotypes rose by 50% after 5 years of the childhood PCV10/13 programme and will most likely continue to increase with more years of PCV10/13 use; these 11 serotypes were responsible for 22–54% of IPD among older adults per site in 2015. A recent meta-analysis assessing indirect PCV effects reported a smaller increase in PPV23non13 serotypes in older adults (IRR 1.18 (1.12–1.25)), but the analysis mixed data across different continents, with variable pre-vaccine and post-PCV10/13 periods.[23] We did not take into account PPV23 use which is recommended for older adults in some countries. As our study period does not cover the years before PPV23 introduction, this could bias our estimates only if PPV23 uptake varied during the study period, which was not the case. Moreover, we did not identify any different trends among PPV23non13 serotypes by PPV23 use, as the sites with the highest uptake (England and Wales, and Scotland, ~70%) had similar IRR to the pooled estimate (1.46 and 1.60, respectively, compared with 1.50).

In 2015 the overall IPD incidence in older adults increased in 12/13 sites compared with 2014 (although 95% CI overlapped in 7/12 sites), almost entirely due to non-PCV13 serotypes. The exception was Norway, but preliminary data suggest that the IPD incidence increased by 18% between 2015 and 2016 because of an increase in IPD due to non-PCV13 serotypes; preliminary data from some sites indicate a further rise in 2016, again due to non-PCV13 serotypes.[5 33 34] Monitoring IPD serotype trends across all age groups in countries with ongoing childhood PCV10/13 programmes is therefore essential.

The reasons for higher pre-vaccine incidence rates in four countries (the Nordic countries and the Netherlands) were not explored in our study. No difference in surveillance sensitivity was identified in these sites, but substantial increases in overall IPD incidence prior to PCV7 introduction (1995–2004) were reported in older adults in these four countries, mostly due to rises in serotypes 1, 4 and 14.[35–39] In other sites with longer pre-PCV7 data in our study, such as the UK and France, IPD incidence rates were stable (figure 1). We hypothesise that regional circulation of specific serotypes or pneumococcal clones caused these higher incidences, although differences in social contact patterns and case detection cannot be excluded.

Our results cannot be easily compared with studies from other sites, which were usually restricted to single sites, included shorter post-PCV13 periods (2–3 years) or used an average incidence over the post-vaccine period.[12 23 25 40] The added value of our study is the pooling of 13 sites from 10 European countries, coverage of five PCV10/13 years and IRR estimations for each PCV10/13 year. There are, however, some limitations. First, methodologies comparing pre- and post-vaccination incidences are prone to biases, whereby changes in other factors over time such as case detection (eg, blood culturing frequency), reporting and other health interventions may be attributed to the vaccination programme. We partly addressed that risk by adjusting for surveillance sensitivity whenever possible. Although we cannot exclude biases due to changes in IPD case detection



*: Sweden and Czech Republic use around 50% PCV10 and 50% PCV13; **: serotypes not in PCV13 and not in PPV23.

Figure 4 Pooled incidence rate ratio per serotype group over the PCV10/13 years compared with 2009 by vaccine policy: SpIDnet/I-MOVE+ multicentre study.

and surveillance, these tend to improve in post-vaccine periods and would underestimate the vaccine effects.[17 19 41] Second, we expect heterogeneity across sites due to differences in healthcare practices, pre-vaccine epidemiology and vaccination policies. We attempted to address this by using random effects meta-analysis and performing stratified analysis by PCV policy. We assumed that these differences across sites would be constant over time, limiting their influence on relative measures of effect such as the IRR. Reassuringly, the τ^2 values suggest limited statistical heterogeneity. Third, the selected pre-PCV10/13 reference period may influence effect estimates. We selected 2009 as the last year before PCV10/13 introduction for all sites, but a single year may be more prone to natural fluctuations. Using the average annual incidence after PCV7 introduction, however, we observed similar patterns in IRR, but with slightly differing values, likely reflecting some additional PCV7 effect on PCV7 and non-PCV7 serotypes in sites with longer periods of PCV7 included in the analysis. We therefore believe that using 2009 as reference provides a more accurate estimate of changes due to PCV10/13 only. Finally, given the variability in pneumococcal serotype epidemiology and PCV history across the participating sites, we cannot infer our findings to the rest of Europe.

CONCLUSION

We report the indirect effect of 5 years of the childhood PCV10/13 programme on the incidence of IPD in older adults across 13 sites in 10 European countries. The large decline in IPD due to vaccine serotypes was partly countered by increases in non-PCV13 serotypes, resulting in a limited net effect on overall IPD. Our findings suggest that the potential benefit of a PCV13 programme in older adults progressively reduces over

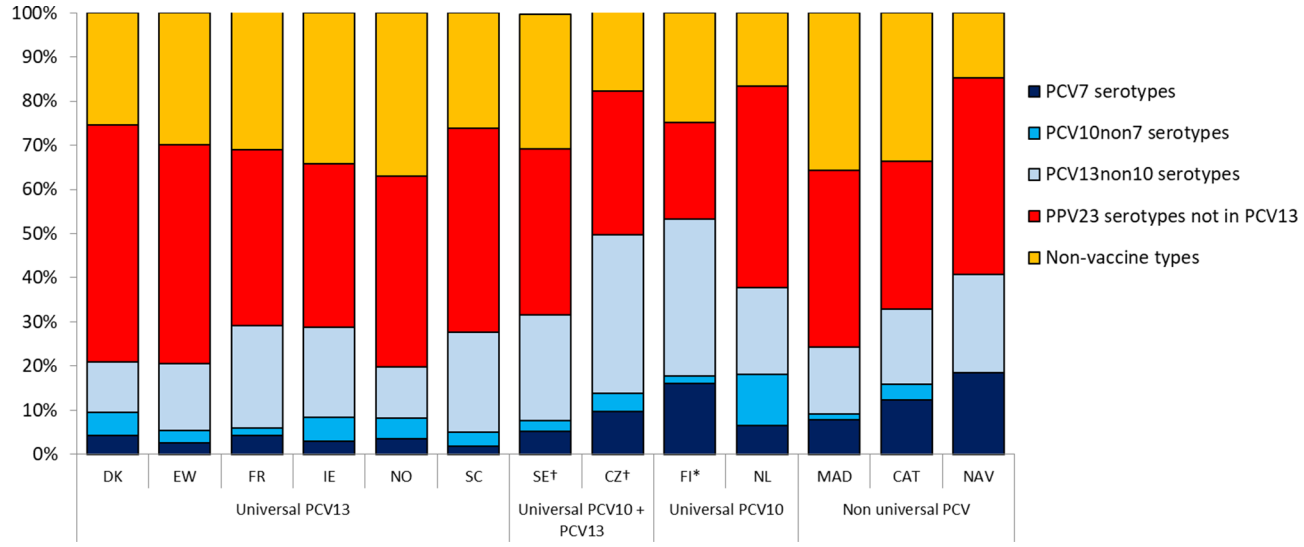


Figure 5 Proportion of serotypes out of all invasive pneumococcal disease in 2015 by serotype group, site and vaccination policies: SpIDnet/I-MOVE+ multicentre study.

time because of the progressive decline in PCV13 serotype IPD and the gradual rise in non-PCV13 serotype IPD across that age group. The substantial and increasing proportion of IPD due to the additional PPV23 serotypes suggests that the advantage of PPV23 over PCV13 in terms of serotypes covered may increase over time in older adults. Our data also suggest that IPD trends in older adults differ according to the childhood PCV used, especially relating to serotype 19A. Policy makers need to take into account the indirect impact of childhood programmes when considering vaccination programmes for older adults in their decision-making process. Our results also indicate that vaccines targeting older adults should include other (or at least more) serotypes, or provide a wider mechanism of protection against pneumococcal disease than against specific capsular serotypes.

The evolution of this indirect effect is difficult to predict. In particular, the consistent observation of an increase in IPD in 2015 across the European sites, the differing trends in serotype 19A and the rise in non-PCV13 serotypes raise concerns. This highlights the need to further monitor IPD serotype trends in future years as more infant cohorts receive PCV10/13.

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Correction notice This article has been corrected since it was published Online First. Some of the information from Figures 4A, 4B and 4C for countries under a universal PCV10 program was missing from the image.

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Contributors GMH performed the statistical analyses of the pooled data and wrote the manuscript. CS was responsible for study coordination, collected data from the SpIDnet sites, contributed to the statistical analyses and writing of the manuscript. SNL and RW contributed to the writing of the manuscript. LPC provided technical support for the study design. PK, PV-B, SNL, NKF, JPN, HR-K, AL, EV, JM, MC, MK, H-CS, AvdE, BAW, DFV, EMD, JK, AS, PC, CM-A, MO, PL, MG, JC, EM and BH-N coordinated the collection, validation and preparation of data at site level. All authors read, commented on and approved all versions of the manuscript. Authors are included in alphabetical order of the country of the participating sites, except for first and last authors.

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REFERENCES

1 Ardanuy C, Marimón JM, Calatayud L, *et al*. Epidemiology of invasive pneumococcal disease in older people in Spain (2007-2009): implications for future vaccination strategies. *PLoS One* 2012;7:e43619.
2 Verhaegen J, Flamaing J, De Backer W, *et al*. Epidemiology and outcome of invasive pneumococcal disease among adults in Belgium, 2009-2011. *Euro Surveill* 2014;19:14–22.
3 Reinert RR, Haupts S, van der Linden M, *et al*. Invasive pneumococcal disease in adults in North-Rhine Westphalia, Germany, 2001-2003. *Clin Microbiol Infect* 2005;11:985–91.
4 Drijkoningen JJ, Rohde GG. Pneumococcal infection in adults: burden of disease. *Clin Microbiol Infect* 2014;20(Suppl 5):45–51.
5 Naucler P, Galanis I, Morfeldt E, *et al*. Comparison of the impact of pneumococcal conjugate vaccine 10 or pneumococcal conjugate vaccine 13 on invasive pneumococcal disease in equivalent populations. *Clin Infect Dis* 2017;65:1780–9.
6 Torres A, Bonanni P, Hryniewicz W, *et al*. Pneumococcal vaccination: what have we learnt so far and what can we expect in the future? *Eur J Clin Microbiol Infect Dis* 2015;34:19–31.
7 European Medicines Agency (EMA). European Public Assessment Report (EPAR) for Prevenar 13. *ANNEX I. Summary of product characteristics*. London: EMA, 2015.
8 Guevara M, Ezpeleta C, Gil-Setas A, *et al*. Reduced incidence of invasive pneumococcal disease after introduction of the 13-valent conjugate vaccine in Navarre, Spain, 2001-2013. *Vaccine* 2014;32:2553–62.
9 Galanis I, Lindstrand A, Darenberg J, *et al*. Effects of PCV7 and PCV13 on invasive pneumococcal disease and carriage in Stockholm, Sweden. *Eur Respir J* 2016;47:1208–18.
10 Waight PA, Andrews NJ, Ladhani SN, *et al*. Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: an observational cohort study. *Lancet Infect Dis* 2015;15:535–43.
11 Harboe ZB, Dalby T, Weinberger DM, *et al*. Impact of 13-valent pneumococcal conjugate vaccination in invasive pneumococcal disease incidence and mortality. *Clin Infect Dis* 2014;59:1066–73.
12 Moore MR, Link-Gelles R, Schaffner W, *et al*. Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: analysis of multisite, population-based surveillance. *Lancet Infect Dis* 2015;15:301–9.
13 Falkenhorst G, Remschmidt C, Harder T, *et al*. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine (PPV23) against pneumococcal disease in the elderly: systematic review and meta-analysis. *PLoS One* 2017;12:e0169368.
14 Moberley S, Holden J, Tatham DP, *et al*. Vaccines for preventing pneumococcal infection in adults. *Cochrane Database Syst Rev* 2013;1:CD000422.
15 European Commission. COMMISSION IMPLEMENTING DECISION of 8 August 2012 amending Decision 2002/253/EC laying down case definitions for reporting communicable diseases to the Community network under Decision No 2119/98/EC of the European Parliament and of the Council. 2012/506/EU. *Official Journal of the European Union* 2012.
16 Halloran ME, Struchiner CJ, Longini IM. Study designs for evaluating different efficacy and effectiveness aspects of vaccines. *Am J Epidemiol* 1997;146:789–803.
17 Hanquet G, Valenciano M, Simondon F, *et al*. Vaccine effects and impact of vaccination programmes in post-licensure studies. *Vaccine* 2013;31:5634–42.
18 Stock NK, Maly M, Sebestova H, *et al*. The Czech surveillance system for invasive pneumococcal disease, 2008-2013: a follow-up assessment and sensitivity estimation. *PLoS One* 2015;10:e0131117.
19 Lepoutre A, Varon E, Georges S, *et al*. Impact of the pneumococcal conjugate vaccines on invasive pneumococcal disease in France, 2001-2012. *Vaccine* 2015;33:359–66.
20 Dorléans F, Mølbak F, Voldstedlund M, *et al*. *Evaluating the completeness of the invasive pneumococcal diseases surveillance system in Denmark, 2010–2011. European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE)*. Stockholm: ECDC, 2013.
21 Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ* 2011;342:d549.
22 Rücker G, Schwarzer G, Carpenter JR, *et al*. Undue reliance on I(2) in assessing heterogeneity may mislead. *BMC Med Res Methodol* 2008;8:79.
23 Shiri T, Datta S, Madan J, *et al*. Indirect effects of childhood pneumococcal conjugate vaccination on invasive pneumococcal disease: a systematic review and meta-analysis. *Lancet Glob Health* 2017;5:e51–e59.
24 D'Ancona F, Caporali MG, Del Manso M, *et al*. Invasive pneumococcal disease in children and adults in seven Italian regions after the introduction of the conjugate vaccine, 2008-2014. *Epidemiol Prev* 2015;39(4 Suppl 1):134–8.
25 van der Linden M, Falkenhorst G, Perniciaro S, *et al*. Effects of infant pneumococcal conjugate vaccination on serotype distribution in invasive pneumococcal disease among children and adults in Germany. *PLoS One* 2015;10:e0131494.
26 Miller E, Andrews NJ, Waight PA, *et al*. Herd immunity and serotype replacement 4 years after seven-valent pneumococcal conjugate vaccination in England and Wales: an observational cohort study. *Lancet Infect Dis* 2011;11:760–8.
27 Grijalva CG, Moore MR, Griffin MR. Assessing the effect of pneumococcal conjugate vaccines: what is the value of routinely collected surveillance data? *Lancet Infect Dis* 2011;11:724–6.
28 Principi N, Esposito S. The impact of 10-valent and 13-valent pneumococcal conjugate vaccines on serotype 19A invasive pneumococcal disease. *Expert Rev Vaccines* 2015;14:1359–66.
29 Verani JR, Domingues CM, de Moraes JC, *et al*. Indirect cohort analysis of 10-valent pneumococcal conjugate vaccine effectiveness against vaccine-type and vaccine-related invasive pneumococcal disease. *Vaccine* 2015;33:6145–8.
30 Bosch A, van Houten MA, Bruin JP, *et al*. Nasopharyngeal carriage of Streptococcus pneumoniae and other bacteria in the 7th year after implementation of the pneumococcal conjugate vaccine in the Netherlands. *Vaccine* 2016;34:531–9.
31 Steens A, Vestrheim DF, de Blasio BF. Pneumococcal vaccination in older adults in the era of childhood vaccination: public health insights from a Norwegian statistical prediction study. *Epidemics* 2015;11:24–31.
32 Corcoran M, Vickers I, Mereckiene J, *et al*. The epidemiology of invasive pneumococcal disease in older adults in the post-PCV era. Has there been a herd effect? *Epidemiol Infect* 2017;145:2390–9.
33 Houseman C, Hughes GJ, Chapman KE, *et al*. Increased invasive pneumococcal disease, North East England, UK. *Emerg Infect Dis* 2017;23:122–6.
34 Ladhani SN, Collins S, Djennad A, *et al*. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000-17: a prospective national observational cohort study. *Lancet Infect Dis* 2018;18:441–51.
35 Henriques Normark B, Kalin M, Ortqvist A, *et al*. Dynamics of penicillin-susceptible clones in invasive pneumococcal disease. *J Infect Dis* 2001;184:861–9.
36 Harboe ZB, Benfield TL, Valentiner-Branth P, *et al*. Temporal trends in invasive pneumococcal disease and pneumococcal serotypes over 7 decades. *Clin Infect Dis* 2010;50:329–37.
37 Pedersen MK, Høiby EA, Frøholm LO, *et al*. Systemic pneumococcal disease in Norway 1995-2001: capsular serotypes and antimicrobial resistance. *Epidemiol Infect* 2004;132:167–75.
38 Spanjaard L, van der Ende A, Rümke H, *et al*. Epidemiology of meningitis and bacteraemia due to Streptococcus pneumoniae in The Netherlands. *Acta Paediatr Suppl* 2000;89:22–6.
39 Vestrheim DF, Høiby EA, Bergsaker MR, *et al*. Indirect effect of conjugate pneumococcal vaccination in a 2+1 dose schedule. *Vaccine* 2010;28:2214–21.
40 Moore CE, Paul J, Foster D, *et al*. Reduction of invasive pneumococcal disease 3 years after the introduction of the 13-valent conjugate vaccine in the Oxfordshire region of England. *J Infect Dis* 2014;210:1001–11.
41 Flasche S, Slack M, Miller E. Long term trends introduce a potential bias when evaluating the impact of the pneumococcal conjugate vaccination programme in England and Wales. *Euro Surveill* 2011;16:19868.