Title: Impact of higher valency pneumococcal conjugate vaccines on invasive pneumococcal disease in children: results of SpIDnet – an observational before/after multicentre study

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Abstract

Background: The *Streptococcus pneumoniae* Invasive Disease network (SpIDnet) conducts active population-based surveillance for invasive pneumococcal disease (IPD) in nine sites from seven European countries. Five sites use 13-valent pneumococcal conjugate vaccine (PCV) only and four use PCV13 and PCV10. Vaccination uptake is >90% in six sites and 67-78% in three sites. We measured the impact of higher valency PCV (PCV13/PCV10) on IPD in children below five years old.

Methods: We compared the IPD incidence between the first four years after PCV13/PCV10 introduction and the average incidence during the period of heptavalent PCV (PCV7) use, overall and by serotype categories. We calculated the pooled incidence rate ratios (IRR) and 95% confidence intervals (CI), using random effects meta-analysis.

Findings: After four years of PCV13/PCV10 use, the pooled IRR was 0·45 for all type IPD, 0·16 for PCV7 serotypes IPD, 0·17 for IPD caused by 1, 5, 7F serotypes, and 0·41 for 3,6A and 19A serotype IPD. Same pattern was observed when restricting to PCV13 sites. The pooled IRR for nonPCV13 serotypes IPD was 1·12, 1·62, 1·64, and 1·62, for each year post PCV13/PCV10 introduction, respectively.

Interpretation: Our results indicate a decrease in all type IPD incidence caused by the decline of vaccine serotypes. This decline was partially countered by the increase in incidence of nonPCV13 serotypes IPD suggesting serotype replacement. Long-term surveillance is needed to monitor the net impact of PCV13/PCV10 infant vaccination programmes.

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Introduction

In Europe, countries introduced pneumococcal conjugate vaccination (PCV) at different times, using various vaccination schedules and targeting different population groups.[1] The introduction of heptavalent pneumococcal conjugate vaccine (PCV7) in the childhood vaccination programmes resulted in a significant decrease in the incidence of invasive pneumococcal disease (IPD) caused by the vaccine serotypes and in an increase of nonPCV7 serotypes such as 19A, 1 or 7F, partly due to the serotype replacement phenomenon.[2-4] In 2009, two higher valency pneumococcal conjugate vaccines (PCV13 and PCV10, panel 1) were licensed in Europe, based on immunogenicity data. These vaccines protect against additional three serotypes (for PCV10) or six serotypes (for PCV13). Some of these serotypes such as 19A and 7F increased substantially after widespread use of PCV7. However, the immunological response to some PCV13 and PCV10 serotypes (common or additional to PCV7) was lower than the established thresholds of protection and the association between surrogate markers of protection and clinical protection was not always consistent in the pre-marketing studies.[5,6]

Monitoring the IPD incidence by serotype in the European Union / European Economic Area (EU/EEA) through sensitive and homogenous surveillance systems is essential to provide robust and precise measurements of the impact of PCV13/PCV10 vaccination strategies and to allow the early detection of potential serotype replacement.[7] The heterogeneity of IPD surveillance systems and data collected by EU/EEA countries hampered the proper evaluation of PCV vaccination policies at European level, at the time PCV7 vaccines became available on the market. Thus, in 2012, the European Centre for Disease Prevention and Control (ECDC) promoted the set-up of SpIDnet (*Streptococcus pneumoniae* Invasive Disease network) to conduct active population-based IPD surveillance in children from ten surveillance sites in eight countries: The Czech Republic, France, Ireland, Norway, Romania, Spain (Catalonia, Madrid, Navarra), Sweden, and the United Kingdom (Scotland). In 2013, seven of these sites had a universal PCV vaccination programme in place (five sites with PCV13 and two with PCV10 and PCV13). The vaccine

uptake exceeded 90% in six sites and 77% in one site (Czech Republic). In two Spanish sites (Navarra and Catalonia), the PCV13/PCV10 pneumococcal vaccination was only covered for high risk groups and recommended by the professional associations in children under five years of age with a vaccine uptake ranging between 67% and 78%. In one site (Romania), the PCV vaccination was included in the national immunisation programme but not funded. No site used PCV10 only, and PCV10 uptake was <50% in the four sites using it (Table 1).

To measure the impact of PCV13/PCV10 vaccination programmes in SpIDnet countries, we compared the IPD incidence in children under five years of age before and after the introduction of PCV13/PCV10 vaccination in the childhood immunisation programmes, pooling surveillance data from SpIDnet sites.

Methods

Nine SpIDnet sites from seven countries (Czech Republic, France, Ireland, Norway, Spain (Catalonia, Madrid, Navarra), Sweden, UK (Scotland)) collected IPD data before and after the introduction of pneumococcal conjugate vaccination programmes up to 2013 inclusive, using a common protocol. This protocol allowed to standardise case definition, laboratory methods, approaches to ensure an active surveillance, data sources, estimation of denominators, completeness and quality of data, and analysis between sites. Romania did not meet the criteria to be included in the impact study.

IPD surveillance systems in the nine SpIDnet sites cover a total of 5·8 million children less than five years of age (Table 1). IPD cases from the catchment areas of participating hospitals or laboratories are regularly reported, and active contact with data providers is organised in each site. IPD cases must meet the ECDC case definition, requiring laboratory confirmation through isolation of *Streptococcus pneumoniae*, detection of bacterial nucleic acid by polymerase chained reaction (PCR) or its antigen in a normally sterile body site. Cases with positive antigen test in urine did not meet the ECDC case definition, therefore were not included in the analysis. The ECDC case definition for IPD remained

unchanged since 2002. National or regional reference laboratories perform serotyping of referred isolates using capsular reaction with specific antisera (Quellung reaction) or PCR. Serotyping by PCR is used in Catalonia, Spain,[8] and for 6A/C differentiation in seven sites. Retrospective differentiation of serotype 6A and 6C was also performed in six sites.

Participating sites reported IPD cases aggregated by age, serotype category and calendar year to SpIDnet coordination (Table 1). We grouped serotypes in five categories and used them throughout the rest of the manuscript: all type IPD, PCV7 serotypes, additional three PCV10/13 (1, 5, 7F) serotypes, additional three PCV13 (3, 6A, 19A) serotypes and nonPCV13 serotypes. Non-typeable serotypes were included in the nonPCV13 category. We assumed that cases with missing serotype information had the same serotype distribution as those with available serotype by site, age and calendar year. For two sites that improved surveillance sensitivity with time (Czech Republic and France), we adjusted the incidence to the sensitivity of surveillance system before and after the introduction of PCV13/PCV10.

We compared the IPD incidence in each year after PCV13/PCV10 introduction to three reference periods: prePCV7 period (years when no conjugate vaccine was used in each site), PCV7 period (years when heptavalent vaccine was used in each site) and the year 2009 (the last year of PCV7 use in seven sites and the only PCV7 year in two sites). The year of introduction of the conjugate vaccine was included in the reference period according to the vaccination coverage level with the respective vaccine (above or below 30% respectively). For each site and period, we calculated the yearly incidence and the average incidence over each period by dividing the number of cases by end-year population data. We calculated the incidence rate ratios (IRR) per site and their 95% confidence intervals (CI). We computed the pooled IRR and the 95% CI by serotype category using random effects meta-analysis. [2] The I-squared test of heterogeneity was calculated using the inverse-variance fixed-effect model.

As primary analysis, we calculated pooled IRR including all reported cases. Subsequently, we performed four sensitivity analyses restricted to IPD cases diagnosed by culture, to the six sites with a PCV13/PCV10 uptake over 90%, to the five sites using PCV13 only, and to six sites with more than two years of PCV7 use.

The impact study was embedded in the IPD surveillance systems and conducted according to the ethical requirements of each participating site. Ethical approval for surveillance activities is not required in any site. We used STATA 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP) for all analyses.

Role of the funding source

This study used IPD surveillance data collected and monitored by each surveillance site according to a ECDC approved standard protocol. The pooled analysis was conducted at the coordination level. ECDC reviewed and approved the study report and the manuscript. The corresponding author had full access to all study data and has the final responsibility of the manuscript. The decision to submit for publication was made by consensus between the coordination, surveillance sites and ECDC. The project received public funding alone.

Results

In the nine SpIDnet participating sites, IPD surveillance data were available for periods ranging from seven years (Czech Republic, Ireland, and Madrid region of Spain) to 14 years (Scotland and France). Seven sites provided data for the prePCV7 period (two to six years) and all sites provided data for the PCV7 period (one to six years). The PCV13/PCV10 period included four years in seven sites, and three years in two sites (Table 1). The median proportion of cases with serotype available varied by site and period, was 87%, ranging from 48% to 100% (Table 2).

The all-type yearly IPD incidence among children less than five years old decreased in all sites in the PCV13/PCV10 period as compared to the prePCV7 and PCV7 periods (Table 2). The pooled IRR of all-type IPD decreased each year after PCV13/PCV10 introduction compared to the PCV7 period and in the first three years as compared to prePCV7 period (Table 3). The PCV7 IPD incidence, that had declined after PCV7 introduction, further decreased after PCV13/PCV10 introduction with a median incidence per 100,000 population of 16·5 (range by site: 7·3-27·3), 3.6 (range: 0-9·7) and 0·5 (range: 0-0·9) in the prePCV7, PCV7 and PCV13/PCV10 periods, respectively. After PCV13/PCV10 introduction, the pooled PCV7 IRR progressively decreased during the PCV13/10 period (Table 3). The median incidence per 100,000 of IPD caused by 1, 5, 7F serotypes together increased from 1·2 (range: 1·1-5·5) in the prePCV7 period to 3·4 (range: 0·3-20·1) in the PCV7 period and declined to 2·1 (range: 0·3-9·8) in the post PCV13/PCV10 period. The IRR for these three serotypes decreased annually after PCV13/PCV10 introduction; the IPD incidence in the fourth year was below the average incidence observed during prePCV7 period (Table 3). For the IPD caused by serotypes 3, 6A, 19A together, the median average incidence per 100,000 also increased from 2·6 (range: 2·0-23·5) prePCV7 to 3·4 (range: 1·0-17·7) in the PCV7 period and declined to 2·4 (range: 1·0-9·3) in the post PCV13/PCV10 period. The related IRR also decreased each year, reaching 0·52 and 0·41 in the fourth PCV13/PCV10 year as compared to prePCV7 and PCV7 periods respectively (Table3). For nonPCV13 serotypes, the median incidence per 100,000 population continuously increased in each period, from 1·8 (range: 0·5-5·1) in the prePCV7 period to 3·5 (range: 1·0-14·5) in the PCV7 period and 6·5 (range: 1·7-11·5) in the post-PCV13/PCV10 period. The pooled IRR for nonPCV13 serotypes increased each year relative to both reference periods, amounting to 2·15, and 1·62 to in the fourth PCV13/PCV10 year as compared to prePCV7 and PCV7 periods respectively. The statistical heterogeneity test exceeded 50% in most analyses (Table 3).

When comparing the incidence in each year post PCV13/PCV10 introduction to the year 2009 as PCV7 reference period, the pooled IRRs were very close to those compared to the average PCV7 period for all

type IPD, additional vaccine serotypes and nonPCV13 serotypes IPD. The higher pooled IRR for PCV7 serotypes when compared to 2009 indicate the additional decrease in this serotypes following PCV7 use (Table 3).

The same pattern in IRR reduction and heterogeneity was observed when restricting the analysis to culture positive IPD cases and to sites with high vaccination uptake (Figure 1, Panel A and B). When restricting the analysis to sites using PCV13 only or sites that used PCV7 for more than two years (Figure 2, Panel C and D) the IRR of serotypes 6A, 3 and 19A IPD was 0·24 (95%CI: 0·13; 0·42) and 0·30 (95%CI: 0·21; 0·42) for the fourth year respectively, compared to 0.41 (95%CI: 0.25; 0.69) for all sites.

Discussion

Our results suggest an overall decrease in all type IPD incidence after introduction of PCV13/PCV10 vaccination, due to a decrease in the incidence of PCV7 and additional serotypes included in higher valency PCV vaccines. NonPCV13 serotypes incidence tended to increase over time compared to both reference periods and represented more than half of all cases in the PCV13/PCV10 period. Pooling data from several European countries enabled the identification of patterns and trends across a wider geographical area and resulted in analyses that are more robust than those performed with data from a single country.

The gradual decrease in overall IPD incidence over the first four PCV13/PCV10 years indicates a positive overall effect of the vaccination programmes.[9] The pooled IRR estimates suggest that replacing PCV7 by PCV13/PCV10 reduced the incidence of all type IPD (-43%) and PCV7 serotypes (-84%) in the fourth year as compared to the average PCV7 period. These values are in line with the percent decline described in the same age group after a similar period of PCV13 use in other countries such as the United States, the United Kingdom and Denmark.[10-12] The additional impact of PCV13/PCV10 on PCV7 serotypes corroborates the high PCV13 effectiveness against PCV7 serotypes reported in several studies.[5,13,14] The

incidence rates of IPD caused by the six additional serotypes of PCV13 vaccines increased in most sites after PCV7 introduction and their trends reversed after PCV13/PCV10 introduction, with a 70% decline in the fourth PCV13/PCV10 year compared to the PCV7 period. The amplitude of this decline is slightly lower than the 80-90% observed in the United States, United Kingdom and Denmark after three or four years of PCV13 use.[10-12,15] This difference may be explained by the high vaccination coverage reached in a short time in these three countries. Indeed, when we restrict the analysis to sites with high vaccination coverage, the decline of the six additional serotypes reached 82% in the fourth PCV13/PCV10 year.

The consistent increase of nonPCV13 serotype incidence in the PCV13/PCV10 period (IRR above one which become statistically significant in year 2 to 4) suggests a role of serotype replacement. Our findings suggest that nonPCV13 rise is plateauing in the years 3 and 4, although it is difficult to conclude that due to overlapping IRR confidence intervals. As we cannot exclude the role of year to year fluctuations, we need additional years of surveillance to better characterize the trends in the nonPCV13 incidence. Other European studies also reported increases in nonPCV13 serotype incidence in children after two to four years of PCV13 use.[10,12,16,17] It has been argued that PCV13/PCV10 have a lower potential to induce serotype replacement of invasive disease than PCV7 because the prevalence of nonPCV13 serotypes in nasopharyngeal carriage reached an equilibrium while the invasiveness of these serotypes might be lower.[18-20] Nevertheless, after the introduction of PCV7 vaccination, serotype replacement, although suspected shortly after the vaccine introduction, was only confirmed few years later. Currently, no consistent emergence of a specific nonPCV13 serotype has been reported across SpIDnet sites or in other reports.[10,11,15-17,19] This is also supported by a higher serotype diversity in all SpIDnet sites (Simpson diversity index ranging between 80% and 95%, with an overall index of 94%) as in another report.[17] Long term monitoring of serotype-specific incidence and carriage prevalence is crucial to better explore the extent and nature of potential serotype replacement after further use of higher valency PCV.

Several limitations of our study should be mentioned. First, we observed a high degree of heterogeneity in IPD incidence across sites. The heterogeneity may be explained by the differences in health care systems (clinical practice), vaccination programmes (PCV7 history, current PCV uptake, use of both PCV10 and PCV13 vaccines (four sites), and proportion of vaccine serotypes covered by the vaccines), case detection and reporting across sites. We believe that the use of a common protocol addressed the differences related to data collection and reporting. The persistence of a high heterogeneity in the sensitivity analyses including only sites with high vaccination coverage, same vaccine (PCV13) or culture positive IPD suggests this is related neither to the vaccine used, nor vaccination uptake, nor to the method of IPD diagnosis. However, despite the high heterogeneity, most site-specific IRR showed the same pattern across sites. This residual heterogeneity might be related to the differences in health care practices such as clinical care protocols, health care access and use of antimicrobials. Even though these may differ between sites, they were assumed constant over time and therefore could not influence the relative measure of the impact. Second, some sites had more than 20% cases with missing serotype information, in spite of increasing serotyping in most sites. We addressed this limitation by assuming the same serotype distribution for the cases with missing serotype information by year, serotype category and site. However, this approach might have other limitations when the number of cases is low (such as not allowing variations when there are zero cases by serotype category). Third, not all sites contributed to year 4 due to different PCV13/PCV10 introduction year, which made difficult the comparison across post-vaccination years. Fourth, this ecological design may partly attribute to vaccination the effects of other factors such as change in the use of antimicrobials or increased awareness of medical professionals. We cannot exclude an increased awareness of clinicians to detect IPD in the post-vaccine period, which would bias toward underestimating PCV impact.

In conclusion, the SpIDnet multicentre surveillance, collecting data using a standardised and common protocol allowed for the measurement of the impact of PCV13/PCV10 on IPD incidence in children from

nine sites of seven European countries. This permitted the quantification of decreases in the vaccine serotype incidence, and identification of an increase in nonPCV13 incidence despite varying serotype dynamics across different countries. Several questions about the effects of higher valency PCV are still pending such as their overall effect on healthy individuals versus populations with underlying conditions, and the extent of their indirect effect. Therefore, continuous high standard active IPD surveillance in children, enhanced surveillance of non-vaccinated age groups, and the inclusion of more sites in SpIDnet is essential to elucidate various aspects of PCV effects on IPD epidemiology. This is intended in the ECDC-funded extended SpIDnet project aiming to evaluate the long-term use of higher valency PCV, until a new generation of vaccines is available.

Author contribution

CS was responsible for the study coordination, design of generic study protocol, collection of data from the SpIDnet sites, statistical analysis of pooled data and writing the first draft of the manuscript. GH, LPC and the members of coordination team provided technical support to study design, analysis and writing the first draft of the manuscript. PK, AL, JM, DFV, PC, MO, MG, EM, EM, JK, EV, SC, BAW, CMA, LG, JC, AS, BHN and members of the SpIDnet surveillance sites adapted the generic protocol to specific sites and coordinated the collection, validation and preparation of data at site level. Members of SpIDnet group read, completed and commented the draft versions of this manuscript. All authors have read, commented and approved the final version of the manuscript. CS had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

CS, PK, AL, JM, DFV, PC, MO, MG, EM, EM, JK, EV, SC, BAW, CMA, LG, JC, AS, BHN, LPC, GH declare no conflict of interest related to this work.

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Research in context

Systematic review on evidence before this study

We searched Pubmed using the following terms: pneumococcal conjugate vaccine and impact/effect with publication date between 1 January 2010 and 8 April 2016 with no language restriction. We screened the title and abstract of 637 articles, assessed 45 full articles and finally included 12 observational studies presenting the impact of higher valency conjugate vaccines on invasive pneumococcal disease incidence in children < 5 years in similar settings as SpIDnet. We excluded studies that did not calculate impact based on incidence rates, studies based on ICD codes without medical validation, conducted in SpIDnet sites or in different settings (outside Europe and North America), or in specific populations at higher risk (i.e. native populations). The included studies (Supplementary table 1) were divided in two categories: non-SpIDnet European studies (six studies) and other studies (six studies).

Added value of this study

This is the first multicentre study presenting quantified impact measures for each of the four years after higher valency PCV introduction. As compared to PCV7 period, the decline in overall IPD incidence was in line with other studies for similar number of years included in the post higher valency PCV period.[11, 12, 21-28] The decrease in all type IPD incidence was however reported to be higher in a PCV10 study (Netherlands, -80%) after three PCV10 years and in one out of three US studies (one using a different method and both using the late PCV7 period not the whole PCV7 period).[25,29] The decrease in vaccine serotypes is in line with the other studies, though a slightly higher decrease is described in the US (explained by the use of the late PCV7 period as reference).[25] The nonPCV13 incidence increase in SpIDnet was similar to the increase observed in England & Wales and Israel after the fourth and second year of PCV13 introduction, respectively;[12, 27] in the other studies the increase in nonPCV13 was non-significant.

Compared to prePCV7 period, our results overall and by serotype in the second year after PCV13/PCV10 introduction were in line with the Israel study,[27] while a European PCV10 study reported a higher decrease in all type IPD and PCV10 serotypes.[30]

Implications of all the available evidence

SpIDnet multicentre study allows to document the gradual decreases in vaccine types and increases in non-vaccine serotypes while more cohorts get vaccinated, and represent an added value compared to studies from single countries when the number of cases is low. Our study also presents data compared to the pre-PCV7 period to allow for quantifying the impact of combined PCV7 and PCV10/13 vaccination, a measure that is rarely made. Harmonizing IPD surveillance or collecting, analysing and presenting data in similar ways can provide additional information on the pneumococcal disease epidemiology in the era of higher valency PCV vaccines.

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List of graphs/tables

Panel 1: Serotypes included in the three pneumococcal conjugate vaccines (PCV) used in vaccination programmes up to present

Vaccine	Serotypes
PCV7	4, 6B, 9V, 14, 18C, 19F, 23F
PCV10	4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F
PCV13	4, 6B, 9V, 14, 18C, 19F, 23F, 1, 3, 5, 6A, 7F, 19A

PCV13, PCV7 (Prevenar 13, Prevenar, Pfizer); PCV10 (Synflorix, GlaxoSmith-Kline)

Table 1: Surveillance characteristics of participating sites, SpIDnet multicentre study

Site / Characteristic	Czech Rep	France	Ireland	Norway	Scotland	Sweden	Catalonia	Madrid	Navarra
Population <5 years covered*	573,939	2,851,051	365,747	313,215	294,281	579,019	413,181	361,374	34,804
Type of the system	Laboratory and hospital based	Hospital and lab-based	Laboratory -based	Laboratory -based	Laboratory - based	Hospital and laboratory - based	Laboratory -based	Hospital and laboratory - based	Hospital and laboratory - based
Case definition	ECDC 2012	ECDC 2012 (except cases diagnosed by antigen detection)	ECDC 2012	ECDC 2012	ECDC 2012	ECDC 2012	ECDC 2012	ECDC 2012	ECDC 2012
PrePCV7 years	2007-2008	1998-2003	2007-2008	2007-2008	2000-2005	2006-2008	NA	NA	2001-2004

Site / Characteristic	Czech Rep	France	Ireland	Norway	Scotland	Sweden	Catalonia	Madrid	Navarra
PCV7 introduction year (schedule)	2005 (3+1)	2003 (3+1) in risk groups 2008 (2+1)	Sep. 2008 (2+1)	2006 (2+1)	2006 (2+1)	2009 (2+1) 2007 - 2008 in some counties	2001 (3+1) for high risk groups	2006 (3+1)	2001 (3+1) for high risk groups
• **years of use**	**2009**	**2004-2009**	**2009-2010**	**2006-2010**	**2006-2009**	**2009**	**2006-2009**	**2007-2009**	**2005-2009**
Higher valency PCV introduction (schedule)	2010 PCV13/PCV10 (3+1)	2010 PCV13 (2+1)	Dec. 2010 PCV13 (2+1)	2011 PCV13 (2+1)	2010 PCV13 (2+1)	2010 PCV13/PCV10 (2+1)	2010 PCV13/PCV 10 (3+1)	2010 PCV13 (2+1)	2010 PCV13/PCV10[†] (3+1)
• **years of use**	**2010-2013**	**2010-2013**	**2011-2013**	**2011-2013**	**2010-2013**	**2010-2013**	**2010-2013**	**2010-2013**	**2010-2013**
PCV13/PCV10 uptake (2013)**	77%	93%	93%	93%	97%	98%	67%	92%	78%

NA=not available; ECDC=European Centre for Disease Prevention and Control; * 2013 end year population; ** Estimated vaccination coverage at 24 months, (SC: primary schedule at 12 months); [†]PCV10 with low coverage.

Table 2. Number of cases, proportion serotyped and all type IPD incidence by site and period in children < 5 years, included in the impact analysis, SpIDnet multicentre study

Sites	Annual average number of cases (median and range % serotyped)			Median (range) annual incidence (per 100,000)		
	prePCV7 period	**PCV7 period**	**PCV13/PCV10 period**	**prePCV7 period**	**PCV7 period**	**PCV13/PCV10 period**
Czech Republic	65 (82, 82:83)	35 (83, one year)	27 (76, 67:83)	12·6 (11·9:13·4)	6·4 (one year)	4·6 (2·6:7·0)
France	480 (NA[£])	461 (NA[£])	346 (NA[£])	18·0 (16·8:19·0)	15·4 (14·0:17·0)	12·1 (8·4:16·9)
Ireland	69 (67, 48:86)	44 (76, 75:77)	41 (63, 59:64)*	21·8 (21·6:21·9)	12·8 (10·1:15·5)	11·5 (10·7:11·8)
Norway	104 (78, 76:80)	52 (95, 92:100)	24 (96, 95:100)*	35·9 (28·9:42·9)	14·1 (9·9:33·1)	8·3 (6·1:9·1)
Scotland, UK	75 (96, 84:97)	41 (95, 92:100)	34 (65, 53:89)	28·8 (19·1:35·8)	12·8 (9·4:23·8)	11·8 (9·5:12·2)
Sweden	81 (88, 81:96)	66 (97, one year)	38 (96, 88:98)	13·9 (13·4:19·9)	12·0 (one year)	6·4 (4·7:9·1)
Catalonia, Spain	NA	231 (75, 68:90)	153 (79, 68:87)	NA	58·7 (50·5:64·4)	38·9 (25·2:41·7)
Madrid, Spain	NA	148 (88, 86:89)	79 (87, 82:87)	NA	41·8 (35·5:51·5)	19·9 (16·0:30·4)
Navarra, Spain	17 (98, 89:100)	14 (90, 57:93)	7 (93, 70:100)	64·3 (33·1:78·2)	42·4 (31·7:61·2)	20·0 (14·5:28·7)

*In Norway and Ireland, the postPCV13/PCV10 period included three years; [£] Data available from two different systems;

NA: not available (prePCV7 data was not available for Madrid and Catalonia, Spain)

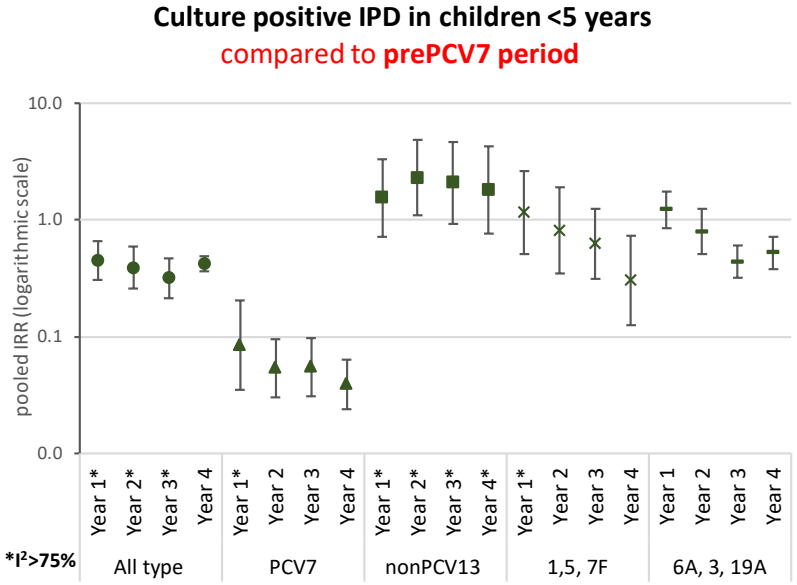
Table 3: Pooled IPD Incidence rate ratio (IRR) in children <5 years by postPCV13/PCV10 year compared to prePCV7 and to PCV7 reference periods, SpIDnet multicentre study

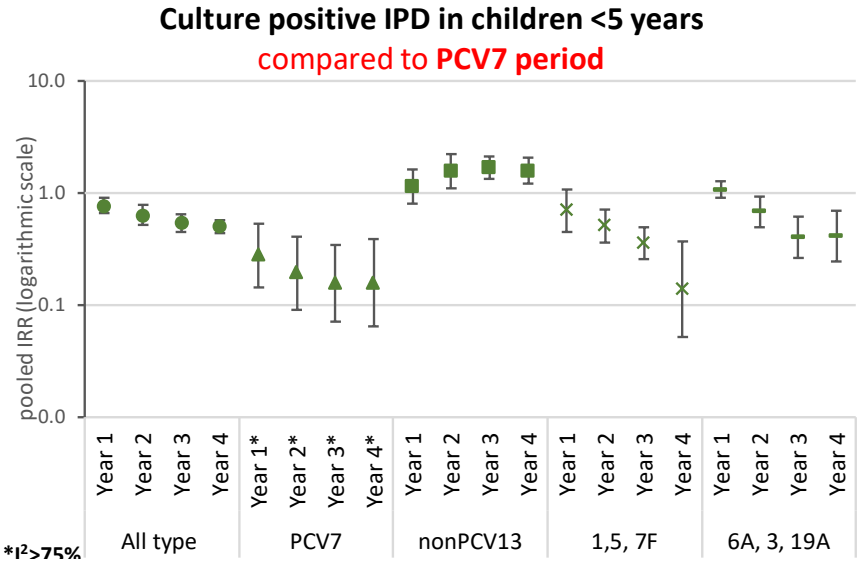
Reference period	IPD serotype categories	Sites year1 (N)	IRR Year 1 postPCV13/ PCV10 (95%CI)	I^2 (%)	Sites year2 (N)	IRR Year 2 postPCV13/ PCV10 (95%CI)	I^2 (%)	Sites year 3 (N)	IRR Year 3 postPCV13/ PCV10 (95%CI)	I^2 (%)	Sites year4 (N)	IRR Year 4 postPCV13/ PCV10 (95%CI)	I^2 (%)
Average	All types	7	0·47 (0·33; 0·68)	86·7	7	0·41 (0·28; 0·60)	87·6	7	0·35 (0·24; 0·50)	83·3	5	0·45 (0·39; 0·51)	0·0
prePCV7	PCV7	7	0·09 (0·04; 0·21)	83·7	7	0·05 (0·03; 0·10)	43·7	7	0·06 (0·04; 0·10)	20·2	5	0·04 (0·03; 0·06)	0·0
period	1, 5, 7F	7	1·18 (0·52; 2·67)	75·9	7	0·84 (0·35; 2·00)	71·1	7	0·68 (0·33; 1·38)	55·1	5	0·36 (0·14; 0·98)	50·3
	3, 6A, 19A	7	1·25 (0·86; 1·82)	38·1	7	0·82 (0·53; 1·27)	37·3	7	0·49 (0·34; 0·71)	16·6	5	0·52 (0·38; 0·71)	0·0
	nonPCV13	7	1·59 (0·75; 3·35)	80·0	7	2·36 (1·14; 4·86)	81·5	7	2·20 (1·06; 4·55)	81·5	5	2·15 (1·06; 4·37)	77·3
Average	All types	9	0·76 (0·65; 0·90)	57·6	9	0·67 (0·56; 0·81)	64·9	9	0·56 (0·45; 0·68)	66·4	7	0·53 (0·43; 0·65)	59·7
PCV7	PCV7	8	0·31 (0·16; 0·59)	80·2	9	0·19 (0·08; 0·45)	83·2	8	0·16 (0·07; 0·34)	77·0	6	0·16 (0·07; 0·40)	79·5
period	1, 5, 7F	9	0·68 (0·43; 1·07)	76·4	9	0·56 (0·41; 0·76)	39·9	9	0·36 (0·25; 0·51)	40·5	7	0·17 (0·07; 0·42)	76·6
	3, 6A, 19A	9	1·06 (0·86; 1·30)	17·8	9	0·71 (0·53; 0·96)	39·2	9	0·46 (0·28; 0·77)	71·3	7	0·41 (0·25; 0·69)	66·5
	nonPCV13	9	1·12 (0·75; 1·67)	67·7	9	1·62 (1·10; 2·40)	78·8	9	1·64 (1·18; 2·27)	59·6	7	1·62 (1·09; 2·42)	70·5

Year 2009	All types	9	0·77 (0·69; 0·86)	19·2	9	0·68 (0·60; 0·78)	31·6	9	0·56 (0·47; 0·66)	53·0	7	0·52 (0·43; 0·64)	61·7
(last PCV7	PCV7	9	0·57 (0·31; 1·06)	69·0	9	0·39 (0·16; 0·94)	80·0	9	0·31 (0·12; 0·81)	80·5	7	0·40 (0·16; 0·98)	72·0
year)	1, 5, 7F	9	0·56 (0·40; 0·77)	56·6	9	0·45 (0·34; 0·58)	31·7	9	0·29 (0·23; 0·36)	5·8	7	0·14 (0·05; 0·37)	80·1
	3, 6A, 19A	9	0·97 (0·76; 1·23)	33·5	9	0·64 (0·47; 0·88)	46·0	9	0·45 (0·25; 0·81)	79·2	7	0·41 (0·22; 0·77)	79·0
	nonPCV13	9	0·99 (0·65; 1·52)	73·4	9	1·44 (0·96; 2·17)	76·5	9	1·43 (1·02; 2·01)	65·3	7	1·42 (0·95; 2·13)	73·7

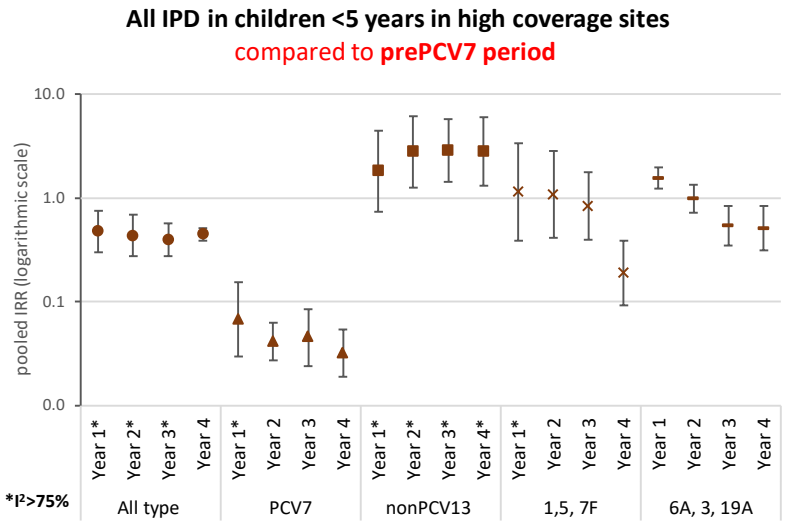
Figure 1: Pooled incidence rate ratios for culture positive IPD cases (Panel A), sites with PCV10/PCV13 vaccination uptake >90% (Panel B), sites with PCV13 only vaccination programme (Panel C), and sites with more than two years of PCV7 use (Panel D), SpIDnet multicentre study (I^2 heterogeneity test; IRR=Incidence Rate Ratio)

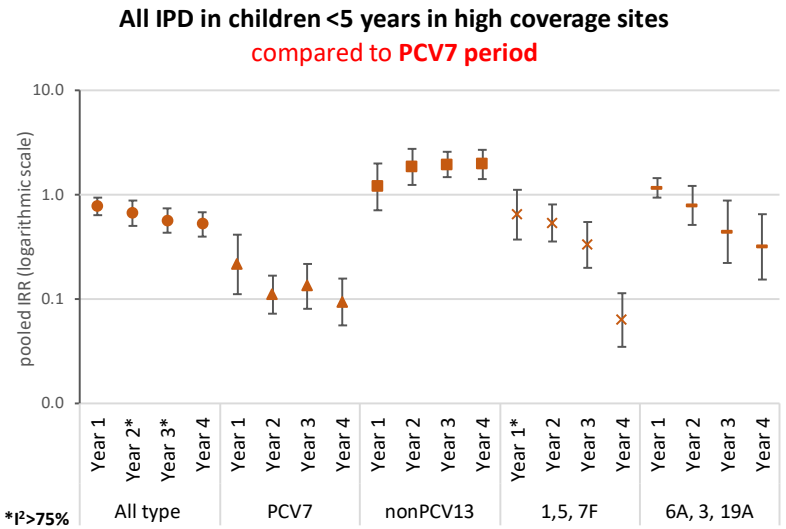
Panel A



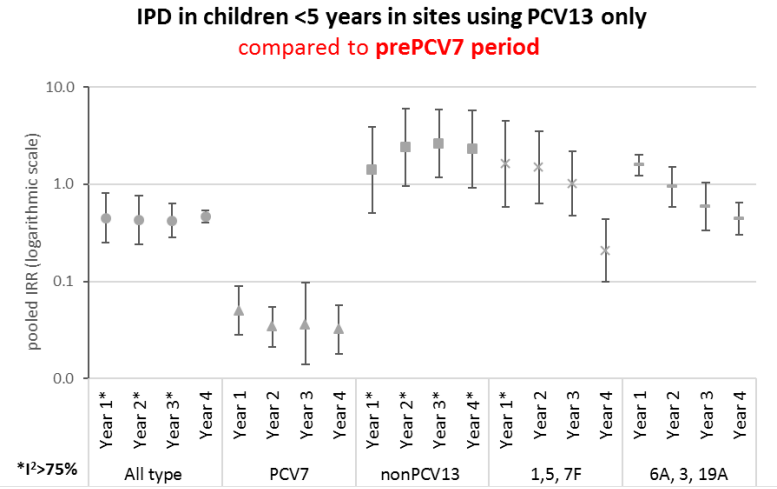


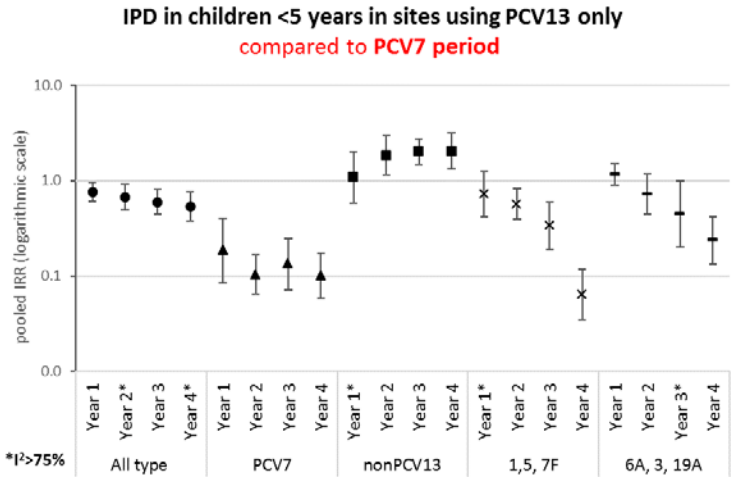
Panel B


All IPD in children <5 years in high coverage sites
compared to prePCV7 period
pooled IRR (logarithmic scale)
10.0
1.0
0.1
0.0
Year 1*
Year 2*
Year 3*
Year 4
Year 1*
Year 2
Year 3
Year 4
Year 1*
Year 2*
Year 3*
Year 4*
Year 1*
Year 2
Year 3
Year 4
Year 1
Year 2
Year 3
Year 4
*I²>75%
All type
PCV7
nonPCV13
1,5, 7F
6A, 3, 19A

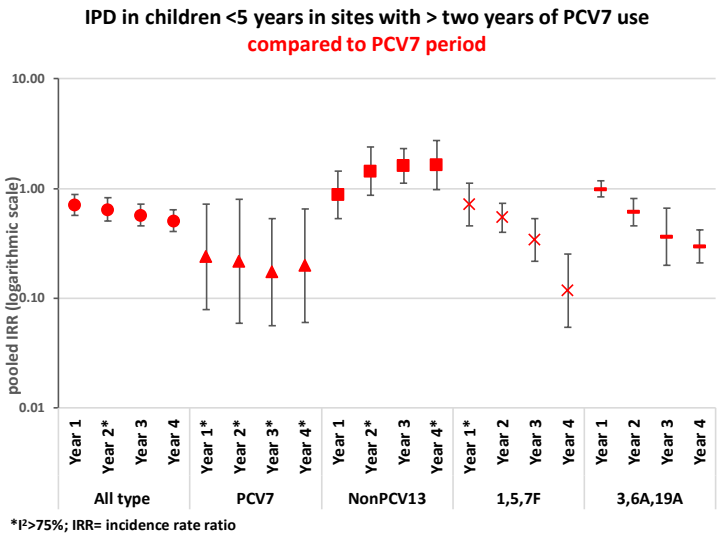

All IPD in children <5 years in high coverage sites
compared to PCV7 period
pooled IRR (logarithmic scale)
10.0
1.0
0.1
0.0
Year 1
Year 2*
Year 3*
Year 4
Year 1
Year 2
Year 3
Year 4
Year 1
Year 2
Year 3
Year 4
Year 1*
Year 2
Year 3
Year 4
Year 1
Year 2
Year 3
Year 4
*I²>75%
All type
PCV7
nonPCV13
1,5, 7F
6A, 3, 19A

Panel C


IPD in children <5 years in sites using PCV13 only
compared to prePCV7 period
pooled IRR (logarithmic scale)
10.0
1.0
0.1
0.0
Year 1*
Year 2*
Year 3*
Year 4
Year 1
Year 2
Year 3
Year 4
Year 1*
Year 2*
Year 3*
Year 4*
Year 1*
Year 2
Year 3
Year 4
Year 1
Year 2
Year 3
Year 4
*I²>75%
All type
PCV7
nonPCV13
1,5, 7F
6A, 3, 19A


IPD in children <5 years in sites using PCV13 only
compared to PCV7 period
pooled IRR (logarithmic scale)
10.0
1.0
0.1
0.0
Year 1
Year 2*
Year 3
Year 4*
Year 1
Year 2
Year 3
Year 4
Year 1*
Year 2
Year 3
Year 4
Year 1*
Year 2
Year 3
Year 4
Year 1
Year 2
Year 3*
Year 4
*I²>75%
All type
PCV7
nonPCV13
1,5, 7F
6A, 3, 19A

Panel D



*I^2>75%; IRR= incidence rate ratio

Supplement Table 1: Summary characteristics of studies retained after the literature review, 2010-2016

Supplement Table 1: Summary characteristics of included studies with invasive pneumococcal disease outcome, 2010-2016

Study ID, country	Data sources	PCV vaccination policy	Schedule	Pre & post vaccination periods	Age groups analyzed	Outcomes analysed	Vaccination coverage (if available)	Comments	Reference	Results in children <5y
Europan non-SpIDnet studies										
Baldovin 2016, Italy	Population-based IPD surveillance, Veneto	PCV7 introduced in 2008 and PCV13 in 2010	NA	2007-2010 2011-2014	All ages	All type IPD, PCV13 IPD, PCV13non7, nonPCV13 IPD			PCV7 period	0-4y: Alltypes: IRR=0.5(0.3-0.7) PCV13: IRR=0.3(0.1-0.5) PCV7: IRR=0.5(0.1-2.8) PCV13non7: IRR=0.2(0.1-0.5) NonPCV13: IRR=1.0 (0.4-2.6)
Sloved 2016, Denmark	Laboratory surveillance system	PCV7 introduced in October 2007 and PCV13 in 2010	2+1 (3, 5, 12 months); catch up for children born after April 2006	1999-2007 2008-2010 2011-2014	All ages	PCV13 IPD, 10 nonPCV13 IPD	Above 80%?		PCV7 period	0-4y: IRR=0.23 (0.02; 2.93)
Knol 2015, Netherlands	Sentinel laboratory surveillance	PCV7 introduced in June 2006 and PCV10 in May 2011	3+1	06/2004-05/2006 06/2009-05/2011 06/2011-05/2013 06/2013-05/2014	All ages	All type IPD, PCV7, PCV10non7, PCV10 related nonPCV10	94%–95%		PrePCV7 and PCV7 period	
	Nationwide laboratory surveillance (<5y)			03/2008–02/2011 03/2011-02/2014	<5y				PCV7 period	Overall -80% decrease IRR not calculated for PCV7 PCV10non7: IRR=0.04 (0.01–0.27) PCV10 related: IRR=0.43 (0.23–0.80) nonPCV10: IRR=0.67 (0.46–0.99)
D'Ancona 2015, Italy	Population-based IPD surveillance, 7 regions	PCV7 introduced in 2008 and PCV13 in 2011	NA	2014 vs 2008	All ages	All type IPD, PCV13 IPD, nonPCV13 IPD	88% (2011) at 24 mo	>50% not serotyped	PCV7 period	0-4y: Alltypes -56% PCV13: -80% NonPCV13: +25%
Waight 2015, UK	Population-based IPD surveillance, England and Wales	PCV7 introduced in September 2006 and PCV13 in April 2010	2+1 (2,4,12 months)	2008-2010 2013-2014	All ages	All type IPD, PCV7 IPD, add6IPD, nonPCV13 IPD	86-90%		PCV7 period	<2y Alltypes:IRR=0.54(0.42–0.69) PCV7: IRR=0.24 (0.06–0.93) PCV13non7: 0.11 (0.06–0.22) NonPCV13: 1.28 (0.94–1.77) 2-4y Alltypes:IRR=0.52 (0.37–0.74) PCV7: IRR=0.20 (0.04–1.12) PCV13non7: 0.09 (0.04–0.25) NonPCV13: 1.71 (1.07–2.81)
Jokinen 2015, Finland	Population-based, observational cohort study	PCV10 introduced in September 2010 No prior use of PCV7	2+1 (3, 5, 12 months) without catch-up campaign	2003-2006 2005-2008 2010-2013	<=5y	PCV10 IPD, PCV10 related IPD, nonPCV10	95%		prePCV10	<=5y: All type IPD: -80% (95%CI 72; 85) PCV10 related: -68(38;85) PCV10 IPD: -92% (95%CI 86 to 95) NonPCV10 IPD: +85 (-243;0, ns)

Supplement Table 1: Summary characteristics of included studies with invasive pneumococcal disease outcome, 2010-2016

Study ID, country	Data sources	PCV vaccination policy	Schedule	Pre & post vaccination periods	Age groups analyzed	Outcomes analysed	Vaccination coverage (if available)	Comments	Reference	Results in children <5y
Other studies										
Bruce 2015, US	Population-based laboratory surveillance, Alaska	PCV7 introduced since 2001; PCV13 in April 2010	3+1	2005-2008 4/2010-2013	All ages	PCV13 IPD, nonPCV13 IPD, All type IPD	86% urban, 92% rural Alaska, 3+ doses 19-35mo (2010). National Immunisation Survey		late PCV7 period	All type IPD <5y: -59% (p=0.002) nonAN PCV13 IPD <5y: -89% (p< 0.001) nonPCV13 IPD +10% (p=0.803) nonAN
Farnham 2015, US	Population-based IPD surveillance in New York	PCV7 introduced since 2001; PCV13 in March 2010	3+1	2007-2009 2011-2012	<5y	PCV13 IPD, nonPCV13 IPD, All type IPD	90% ≥1 dose		late PCV7 period	All type IPD: -70% (–79.3; –55.5) PCV13 IPD: -82.5% (–90.0; –69.3)
Moore 2015, US	Population and laboratory-based IPD surveillance, ABC surveillance	PCV7 introduced since 2000; PCV13 in 2010	3+1 (2, 4, 6, and 12-15 mo)	2004-2010 (Expected) 2010-2013 (Observed)	All ages	All type IPD, PCV7+6A, PCV13non7non6A, nonPCV13	76% 3 doses+	Expected: modelled of 2004-2010 data in the absence of PCV13	late PCV7 period	<5y: All type IPD: y1: –45% (–50;–40) y2: –58% (–63;–53) y3: –64% (–68; –59) PCV13non8 IPD: y1: –66% (–70; –61) y2: –88% (–89; –86) y3: –93% (–94; –91) NonPCV13: y1: –4% (–16; 12) y2: 7% (–9; 31) y3: –2% (–19; 27)
De Wals 2014, Canada, Quebec	Laboratory surveillance	PCV7 introduced for all children 2004 (catch-up<5y), PCV10 in summer 2009 and PCV13 in January 2011.	2+1 (2, 4 and 12 months)	2007-2009, 2010-2011	All ages	All type IPD, PCV7 IPD, PCV10 IPD, 19A IPD, nonPCV10non19A IPD	97% of infants are vaccinated by age 24 months and 93% for the recommended number of doses	cohorts <2 y	PCV7 period	<2y: All types: -45% PCV7: -7% PCV10: -77% Other types: -47%
Andrade 2016, Brazil	Meningitis and IBD databases linkage	PCV10 introduced in March 2010	3+1 (2, 4 and 6 months plus a booster at 12 months); catch up for 7-11 months (2+1) and 12-23 months (1 dose)	2008-2009 2011-2013 2010 (transition period)	All ages	All type IPD	82%, 88%, and 92% for the years 2011, 2012 and 2013	interrupted time series analysis (observed and predicted compared)	prePCV10	All type IPD 2-23mo: -44.2% (-72.5;15.8) 2-4y:+14.7 (-85.7; 115.1)
Ben-Shimol 2014, Israel	Pediatric active IPD surveillance	PCV7 introduced to NIP in July 2009, PCV13 replaced it starting November 2010.	2+1 (2, 4 and 12 months)	07/2004-06/2008 07/2010-06/2011 07/2012-06/2013	Children<5y	All type IPD, PCV7+6A IPD, add5IPD, nonPCV13 IPD	>70% of children 12–23mo vaccinated with ≥2 PCV7 doses		prePCV7 PCV7 period	<5y: All types prePCV7: IRR=0.37 (0.31–0.45 PCV7: IRR=0.58 (0.47–0.70) PCV7+6A: prePCV7: IRR= 0.05 (0.03–0.09) PCV7: IRR=0.47 (0.23–0.93) PCV5: prePCV7: 0.30 (0.21–0.44) PCV7: 0.21 (0.15–0.30) NonPCV13 prePCV7: IRR=2.43 (1.73–3.66) PCV7: IRR=1.61 (1.18–2.19)