

Title

Effectiveness of 10 and 13-valent pneumococcal conjugate vaccines against invasive pneumococcal disease in European children: SpIDnet observational multicentre study

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51 **Abbreviations**

- 52 • PCV10: 10-valent pneumococcal conjugate vaccine
- 53 • PCV13 : 10-valent pneumococcal conjugate vaccine
- 54 • IPD : invasive pneumococcal disease
- 55 • SplDnet : *Streptococcus pneumoniae* Invasive Disease Network

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Abstract (300 words)

Background: Pneumococcal conjugate vaccines covering 10 (PCV10) and 13 (PCV13) serotypes have been introduced in the infant immunization schedule of most European countries in 2010-11. To provide additional real-life data, we measured the effectiveness of PCV10 and PCV13 against invasive pneumococcal disease (IPD) in children of 12 European sites (SpIDnet).

Methods: We compared the vaccination status of PCV10 and PCV13 serotype IPD (cases) to that of nonPCV13 serotype IPD (controls) reported in 2011-2018. We calculated pooled effectiveness as $(1 - \text{vaccination odds ratio}) \times 100$, and measured effectiveness over time since booster dose.

Results: The PCV13 and PCV10 studies included 2522 IPD cases from ten sites and 486 cases from four sites, respectively. The effectiveness of ≥ 1 PCV13 dose was 84.2% (95%CI: 79.0-88.1) against PCV13 serotypes (n=2353), and decreased from 93.1% (87.8-96.1) <12 months to 85.1% (72.0-92.1) ≥ 24 months after booster dose. PCV13 effectiveness of ≥ 1 dose was 84.7% (55.7-94.7) against fatal PCV13 IPD, 64.5% (43.7-77.6), 83.2% (73.7-89.3) and 85.1% (67.6-93.1) against top serotypes 3, 19A and 1, respectively, and 85.4% (62.3-94.4) against 6C. Serotype 3 and 19A effectiveness declined more rapidly. PCV10 effectiveness of ≥ 1 dose was 84.8% (69.4-92.5) against PCV10 serotypes (n=370), 27.2% (-187.6 to 81.6) and 85.3% (35.2-96.7) against top serotypes 1 and 7F, 32.5% (-28.3 to 64.5) and -14.4% (-526.5 to 79.1) against vaccine-related serotypes 19A and 6C, respectively.

Conclusions: PCV10 and PCV13 provide similar protection against IPD due to the respective vaccine serotype groups but serotype-specific effectiveness varies by serotype and vaccine. PCV13 provided individual protection against serotype 3 and vaccine-related serotype 6C IPD. PCV10 effectiveness was not significant against vaccine-related serotypes 19A and 6C. PCV13 effectiveness declined with time after booster vaccination. This multinational collaboration enabled measuring serotype-specific vaccine

80 effectiveness with a precision rarely possible at the national level. Such large networks are crucial for
81 the evaluation of new PCVs.

82 **Keywords:**

83 *Streptococcus pneumoniae*

84 Pneumococcal Infections

85 13-valent pneumococcal vaccine

86 10-valent pneumococcal vaccine

87 invasive pneumococcal disease

88 serotype

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INTRODUCTION

In Europe, the authorisation of 10- and 13-valent conjugate pneumococcal vaccines (PCV10 and PCV13, Table 1) in 2009 was based on immunogenicity data.¹ However, the serotype-specific antibody responses to some of the vaccine serotypes was lower when compared to serotypes shared with the heptavalent PCV (PCV7), and the association between surrogates markers of protection and clinical protection was not always consistent.²⁻⁴ The protection conferred by these vaccines against specific vaccine and vaccine-related serotype¹disease and the duration of protection in real life settings, are still insufficiently documented.⁴⁻⁷ In particular, serotype 3 IPD incidence increased in recent years in many European countries, and PCV13 effectiveness against this serotype is inconsistent across national studies and often lacks precision.^{6,7} Similar observations have been made for vaccine-related serotype 19A in countries using PCV10. The cross-protection of PCV10 and PCV13 against serotype 6C IPD has been estimated in only a few studies,^{7,10} and this serotype tended to increase in countries or regions using PCV10.¹¹⁻¹³

Table 1: Serotypes included in the three pneumococcal conjugate vaccines (PCV) used in vaccination programmes up to 2020

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*).

¹ Protection against disease caused by serotypes belonging to the same serogroup as the vaccine serotypes

108 Since 2010, PCV10 and PCV13 have been widely used in Europe. SplDnet, a network of 11 European
109 countries was set up in 2012 to enhance population-based IPD surveillance to measure the impact and
110 effectiveness of pneumococcal vaccination programmes using PCVs, and 9 countries (12 sites)
111 participated in the effectiveness study.^{14 15} In 2018, a universal PCV vaccination programme was in place
112 in the nine countries (six with PCV13, two with PCV10 and one with both). In seven countries with a
113 universal programme (Denmark, Finland, France, Ireland, Netherlands, Norway, United Kingdom),
114 vaccine uptake exceeded 90% for the schedule including two priming and one booster dose (2+1); two
115 of those used PCV10 and the other five used PCV13 (Table 2). In the Czech Republic, universal
116 vaccination with PCV10 was reimbursed by insurance companies with a schedule including three priming
117 and one booster doses (3+1), but parents could cover the price difference for PCV13 vaccination; this
118 has led to equal use of PCV10 and PCV13 with an overall uptake of 67-81% (2012-2018). Among the
119 three Spanish sites, PCV was either recommended by the professional associations or covered by the
120 regional administration (depending to available regional funding) with a 3+1 schedule until 2016 when a
121 universal vaccination programme was instituted with a 2+1 schedule; vaccine uptake varied between 50-
122 92% during 2012-2018.

123 Table 2: PCV programme, uptake and history by site, 2011-2018, in 12 SplDnet sites.

Site	Introduction of childhood PCV7	Introduction of childhood PCV10/PCV13 and schedule	2011	2012	2013	2014	2015	2016	2017	2018
CZ	Not universal, recommended and used in 2009	Universal PCV10 and PCV13 in 2010 (~equal shares), 3+1 doses	81%	80%	77%	74%	71%	68%	67%	64%
DK	In 2007, universal	Universal PCV13 in 2010, 2+1 doses	89%	90%	91%	91%	91%	94%	96%	96%
EN	In 2006, universal	Universal PCV13 in 2010, 2+1 doses	94%	94%	94%	94%	94%	94%	93%	93%
FI	Not introduced	Universal PCV10 in 2010, 2+1 doses	90%	94%	94%	95%	96%	96%	96%	94%
FR	In 2003 for children at risk, in 2006 for all <2 years	Universal PCV13 in 2010, 2+1 doses	94%	94%	95%	94%	95%	96%	95%	98%

IE	In 2008, universal	Universal PCV13 in 2010, 2+1 doses	90%	93%	93%	92%	93%	91%	90%	93%
NL	In 2006, universal	Universal PCV10 in 2011, 2+1 doses	95%	95%	95%	94%	94%	94%	93%	93%
NO	In 2006, universal	Universal PCV13 in 2011, 2+1 doses	93%	93%	93%	93%	93%	94%	92%	93%
SC	In 2006, universal	Universal PCV13 in 2010, 2+1 doses	94%	95%	96%	96%	95%	95%	95%	95%
CAT	In 2001 for high risk groups and recommended for all*	PCV13 recommended since 2010, universal since 2016, 3+1 doses†	±50%	±50%	±50%	±50%	73%	73%	82%	93%
MAD	In 2006, universal	Universal PCV13 in 2010, interrupted in 2012-2014, 2+1 doses	100%	92%	77%	77%	99%	99%	92%	96%
NAV	In 2001 for high risk groups and recommended for all*	PCV13 recommended since 2010, universal since 2016, 3+1 doses†	70%	73%	75%	78%	81%	88%	88%	81%

According to national and ECDC reports. CAT: Catalonia; CZ: Czech Republic; DK: Denmark; EN: England; FI: Finland; FR: France; IE: Ireland; MAD: Madrid; NAV: Navarra; NL: the Netherlands; NOR: Norway; SC: Scotland; SE: Sweden. PCV: pneumococcal conjugate vaccine; PCV7: 7-valent PCV; PCV10: 10-valent PCV; PCV13: 13-valent PCV; PPV23: 23-valent polysaccharide vaccine. *recommended by paediatricians and not funded, uptake around 50%. †PCV13 was used almost exclusively, the PCV10 uptake in children <2 years was minimal (<1% in NAV and <5% in CAT).

Monitoring serotype-specific effectiveness for PCVs at a population level is a critical component of post-marketing surveillance to provide information for decision making on vaccine policies and to design more effective vaccines.^{1 16} The ability of PCV programmes to reduce the incidence of vaccine-serotype IPD in Europe resulted in an insufficient number of cases to estimate with precision serotype-specific vaccine effectiveness at the national level for most countries, as well as the waning of protection over time. Pooling surveillance data from SpIDnet sites, we measured the effectiveness of PCV10 and PCV13 against vaccine serotype IPD overall and by serotype, over time, as well as against clinical presentation and antimicrobial susceptibility) to provide robust evidence for IPD control and PCV decision making, that national studies alone cannot generate.

MATERIALS AND METHODS

Twelve sites from 10 countries participated in the SpIDnet multi-centre effectiveness studies. Eight sites collected IPD data as part of prospective active surveillance during 2012-2018. Three sites that joined in 2015 and one site that joined in 2017, provided retrospective data for the period 2011-2018 using the

same protocol adapted to each site setting

(https://www.ecdc.europa.eu/sites/default/files/documents/SpIDnet_Protocol_enhanced_surveillance-2018.pdf).

IPD surveillance in SpIDnet sites

IPD surveillance was comprehensive in each site and based on the mandatory notification in 8 of the 12 sites. Surveillance is conducted at national level in 6 sites and at regional level in 6 sites (including England and Scotland). IPD surveillance across the 12 sites covered a population of 6.9 million children under five years of age. IPD cases from catchment areas of participating hospitals or laboratories were identified according to the European Union case definition

(<https://www.ecdc.europa.eu/en/surveillance-and-disease-data/eu-case-definitions>). National or regional reference laboratories performed either phenotypic or genotypic based serotyping of referred *S. pneumoniae* isolates.¹⁷

The participating sites collected case-based data on disease (confirmation date, serotype, clinical presentation, admission to the intensive care unit, outcome, antimicrobial susceptibility), vaccination (date of vaccination, number of doses, brand) and underlying conditions (according to the risk groups for pneumococcal infection in each site).

Study design and population

We measured PCV13 and PCV10 effectiveness using the indirect cohort (Broome) method.¹⁸ This design compares the vaccination status of vaccine-serotype IPD (cases) to that of non-vaccine serotype IPD (controls). We included IPD cases if they were eligible for at least one dose of vaccine at disease onset (aged 2/3-59 months), met the IPD European case definition and had the serotype identified. We excluded cases with contraindication to PCV, no vaccination status available or if vaccinated with PCV7

only. For PCV13 effectiveness, we excluded cases vaccinated with PCV10. We also excluded from the control group PCV13-related serotypes (i.e. serotype with the same serogroup as the vaccine serotypes). For PCV10 effectiveness analysis, we excluded children vaccinated with PCV13. We excluded from the control group serotypes 6A, 3 and 19A, to obtain a comparable reference group in both analyses.

Outcome

In the PCV13 effectiveness analysis, we measured effectiveness against specific outcomes such as vaccine and vaccine-related serotype IPD, clinical manifestations and severity as well as pneumococcal antimicrobial non-susceptibility. To measure effectiveness against specific clinical manifestations, we restricted the analysis to meningitis and invasive pneumonia (bacteremic pneumonia and pleural effusions including empyema). For severity, we measured effectiveness against PCV13 IPD-related deaths and admission to intensive care unit (ICU). For antimicrobial susceptibility, we restricted the analysis to cases with positive cultures and we used the EUCAST clinical thresholds (version 10) for penicillin (minimum inhibitory concentration (MIC) >0.06 mg/L), erythromycin (MIC>0.25 mg/L), and ceftriaxone (MIC >0.5mg/L). Non-susceptibility included both intermediate and resistant strains.

Exposure

Whenever the sample size allowed, we measured effectiveness for at least one dose and complete vaccination according to the schedule in place at each site. We defined “at least one dose” as receiving PCV at least 14 days before onset of symptoms, admission, diagnosis or IPD notification to the surveillance site, regardless of age. Children receiving no dose or one PCV dose within 14 days before disease date were considered unvaccinated. We defined “complete vaccination” as children aged 12-59 months who had received the primary schedule and a booster according to the vaccination policy in each site, or who were recorded as fully vaccinated in the surveillance system. Children with missing

date of vaccination or number of vaccine doses received were included in the “uncertain” vaccination category and excluded from the analyses using “complete vaccination” as exposure. For the PCV13 effectiveness analysis per dose and schedule, we included IPD cases with available information on number of doses and date of vaccination. IPD cases were assigned to different categories (one to three doses below one year, 2+1, 3+1) according to the age and number of doses received. To measure PCV13 effectiveness by time since vaccination, we included children eligible for the booster dose (12-59 months) who had a complete immunisation history recorded. We defined time since vaccination as the number of months between the available date of onset/admission/diagnosis/notification and the date of the booster.

Statistical analysis

We compared cases and controls by baseline characteristics (site, age, gender, underlying conditions) using the chi-square test or Fisher’s exact test as appropriate. PCV effectiveness was calculated as $100\% \times (1 - \text{odds of vaccination for cases} / \text{odds of vaccination for controls})$. We used logistic regression, or penalised logistic regression when we had less than 10 cases per parameter. We adjusted for site (as fixed effect), age in years and year of notification for both vaccines. Sites were included if they had at least one case included in the specific analysis. We adjusted for underlying conditions in the PCV13 analysis but not in the PCV10 analysis as underlying conditions variable was not provided in two of the four sites included in the PCV10 analysis. We also performed a sensitivity analysis by excluding cases from England.

To analyse the effectiveness by time since vaccination, we stratified the months since vaccination into three or four categories: <12, 12-23, 24 + (24-35, ≥ 36) months since vaccination and reported results that provided the best data fit according to Akaike information criterion (AIC). We used the Wald test to

compare the results by strata of time since vaccination and schedule. To obtain a better fit for the data, we also modelled months since vaccination as restricted cubic spline with an interaction between spline and vaccination (n=4 knots automatically selected by the model), with 0 months allocated to unvaccinated.

To assess the bias that the Broome method could introduce due to serotype replacement, when vaccination could increase the risk of infection with non-vaccine pneumococcal serotypes among vaccinated, we used the formula provided by Andrews *et al.*¹⁹

We used Stata 15 for all analyses (College Station, TX: StataCorp LLC, 2017).

This analysis 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.

RESULTS

The 12 participating sites reported 4684 hospital-attended IPD cases in children aged <5 years during the study period. The cumulative number of cases varied between 68 in Navarra, Spain to 1690 in England, UK.

PCV13 effectiveness

IPD cases from 10 sites using PCV13 in their national immunisation programme were analysed. Of the 3483 (74%) eligible cases, 2805 (81%) were included in the final analysis: 600 PCV13 IPD, 283 vaccine-related IPD cases and 1922 nonPCV13 controls (Figure 1). Among the PCV13 cases, serotype 3 ranked first with 161 (27%) cases, followed by serotypes 19A (n=156, 26%), 14 (n=67, 11%) and 1 (n=61, 10%); the remaining vaccine serotypes represented 26% (n=155) of cases. Among the nonPCV13 controls, the

leading serotypes were 24F (n=285, 15%), 15B/C (n=237, 12%), 12F (n=234, 12%) and 10A (n=193, 10%), with 31 other serotypes each representing <10% of controls (Figure 1). PCV13 cases were older and had a lower proportion of underlying co-morbidities than controls (Table 3).

Table 3: Comparison of PCV13 cases and nonPCV13 controls, 2012-2018, SpIDnet multi-centre study

Characteristics (n)	PCV13 IPD 600	%	NonPCV13 controls 1922	%	p value
Age group					<0.0001
• 2-23 months	293	48.8	1331	69.3	
• 24-59 months	307	51.2	591	30.7	
Gender					0.300
• female	246	41.0	834	43.4	
• male	354	59.0	1088	56.6	
Underlying diseases					<0.0001
• no	524	87.3	1481	77.1	
• yes	76	12.7	441	22.9	
Year of notification					
• 2012	131	21.8	199	10.4	
• 2013	108	18.0	249	13.0	
• 2014	84	14.0	285	14.8	
• 2015	80	13.3	357	18.6	
• 2016	73	12.2	268	13.9	
• 2017	70	11.7	305	15.9	
• 2018	54	9.0	259	13.5	
Site					
• Czech Republic	38	6.3	21	1.1	
• Denmark	15	2.5	133	6.9	
• France (three regions in North-West, ACTIV)	19	3.2	95	4.9	
• Ireland	25	4.2	65	3.4	
• Norway	10	1.7	66	3.4	
• Catalonia	251	41.8	207	10.8	
• Madrid	41	6.8	236	12.3	
• Navarra	19	3.2	35	1.8	
• Scotland	12	2.0	72	3.7	
• England	170	28.3	992	51.6	
Outcome					0.629
• alive	561	93.5	1766	91.9	
• death	21	3.5	76	3.95	
• missing	18	3.0	80	4.16	
Admission in intensive care unit*					0.455
• no	306	72.9	571	66.1	
• yes	71	16.9	117	13.5	
• missing	43	10.2	176	20.4	

Characteristics (n)	PCV13 IPD 600	%	NonPCV13 controls 1922	%	p value
Clinical presentation					
• meningitis	70	11.7	464	24.1	<0.0001
• pneumonia	344	57.3	533	27.7	<0.0001
Vaccination status					<0.0001
• at least one dose PCV13	321	53.5	1777	92.5	
○ fully vaccinated	163	27.2	850	44.2	
○ partially vaccinated	136	22.7	829	43.1	
○ uncertain schedule	22	3.7	100	5.2	
• unvaccinated	279	46.5	145	7.5	

*provided by 8 sites (n=1284); IPD: invasive pneumococcal disease; ICU: intensive care unit.

The adjusted PCV13 effectiveness against IPD caused by PCV13 serotypes was 84.2% (79.0-88.1) for at least one dose and 88.7% (81.7-92.7) for the complete vaccination (Table 4). With a 65.8% of PCV13 serotypes in unvaccinated in our study and a high case carrier ratio of vaccine serotypes, we may have overestimated PCV13 effectiveness by <5% (Figure 2). PCV13 effectiveness point estimates against PCV7 serotype IPD were 93.0% and 96.1%, respectively, and, for additional six PCV13non7 serotypes, 79.0% and 83.4%, respectively (Table 4). The adjusted PCV13 effectiveness against vaccine-related serotypes was 52.6% for at least one dose and 64.0% for the complete schedule. The adjusted PCV13 effectiveness point estimates exceeded 80% against serotypes 19A, 1, 7F, 14, 19F, 9V for at least one dose and the complete schedule with inferior limit of confidence interval above 68%. PCV13 effectiveness for at least one dose and complete schedule was, respectively, 64.5% (43.7-77.6) and 65.5% (34.4-81.8) against serotype 3 IPD, respectively, 85.4% (62.3-94.4) and 93.7% (67.7-98.8) against vaccine-related serotype 6C, and 40.1% (-6.3 to 66.3) and 59.4% (14.3-80.8) against vaccine-related serotype 23B. The point estimates of PCV13 effectiveness were above 80% against PCV13 serotype meningitis, pneumonia and above 85% against severe IPD. Similarly, effectiveness against PCV13 IPD by antimicrobial susceptibility was above 90% for the three antimicrobials analysed, for both susceptible and non-susceptible strains. The PCV13 effectiveness point estimates of different PCV13 schedules against PCV13 serotype IPD were

250 60.6% and 76.1% after one and two doses administered under one year of age, respectively, and 95.6%
251 for the third dose (in a 3+1 schedule) administered at 6-11 months of age. After a booster dose, the
252 effectiveness point estimates were 78.2% for 2+1 and 89.7% for 3+1 schedule ($p=0.07$) (Table 4).
253

254 Table 4: Vaccine effectiveness (VE) for PCV13 by outcome and schedule, SplDnet multicentre study,
255 2012-2018

Outcome	Number of sites included	Exposure	Total	PCV13 IPD cases / vaccinated	NonPCV13 controls / vaccinated	PCV13 adjusted VE* (%)	LCI (%)	UCI (%)
Serotype groups								
PCV13	10 sites	at least one dose	2522	600/321	1922/1777	84.2	79.0	88.1
	10 sites	complete vaccination	1273	372/162	901/836	88.7	82.7	92.7
PCV13non7	10 sites	at least one dose	2353	431/268	1922/1777	79.0	71.3	84.7
	10 sites	complete vaccination	1166	265/138	901/836	83.4	73.5	89.6
PCV10non7	9 sites	at least one dose	1703	102/45	1601/1467	88.0	79.1	93.1
	7 sites	complete vaccination	638	66/22	572/525	87.2	70.7	94.4
PCV7	10 sites	at least one dose	2091	169/53	1922/1777	93.0	89.1	95.5
	10 sites	complete vaccination	1008	107/24	901/836	96.1	92.2	98.0
Vaccine-related serotypes	10 sites	at least one dose	2205	283/246	1922/1777	52.6	27.3	69.1
	10 sites	complete vaccination	1051	150/128	901/836	64.0	33.2	80.6
Specific serotypes								
<i>- Vaccine serotypes</i>								
Serotype 3	10 sites	at least one dose	2083	161/118	1922/1777	64.5	43.7	77.6
	9 sites	complete vaccination	975	100/67	875/813	65.5	34.4	81.8
Serotype 19A	10 sites	at least one dose	2078	156/101	1922/1777	83.2	73.7	89.3
	10 sites	complete vaccination	993	92/49	901/836	89.1	79.5	94.2
Serotype 19A without England	9 sites	at least one dose	1027	97/50	930/836	87.8	80.3	94.0
	9 sites	complete vaccination	472	59/21	413/361	92.0	81.7	96.5
Serotype 1	6 sites	at least one dose	1242	61/26	1181/1080	85.1	67.6	93.1
	5 sites	complete vaccination	586	51/18	535/430	85.4	62.5	94.3
Serotype 7F	7 sites	at least one dose	1441	40/18	1401/1286	91.4	81.7	95.9
	5 sites	complete vaccination	462	15/4	447/408	94.1	75.9	98.6
Serotype 14	7 sites	at least one dose	1483	67/8	1416/1298	96.8	92.8	98.6
	7 sites	complete vaccination	709	50/3	659/606	97.6	92.2	99.3
Serotype 19F	10 sites	at least one dose	1972	50/30	1922/1777	84.4	68.9	92.2
	7 sites	complete vaccination	844	23/13	821/771	92.3	75.7	97.5
Serotype 6A/B	6 sites	at least one dose	1469	27/9	1442/1320	92.7	82.1	97.1
	4 sites	complete vaccination	463	12/1	451/406	95.9	71.5	99.4
Serotype 9V	3 sites	at least one dose	865	14/2	851/773	97.3	84.6	99.5
	3 sites	complete vaccination	421	11/2	410/373	97.4	77.3	99.7
<i>- Vaccine-related serotypes</i>								
- Serotype 23B	10 sites	at least one dose	2094	172 2 /105	1922/1777	40.1	-6.3	66.3
	10 sites	complete vaccination	1004	103/91	901/836	59.4	14.3	80.8
- Serotype 6C	7 sites	at least one dose	1654	25/17	1629/1508	85.4	62.3	94.4
	5 sites	complete vaccination	666	11/7	655/625	93.7	67.7	98.8
Clinical presentations due to PCV13 serotype IPD								
PCV13 meningitis	10 sites	at least one dose	534	70/43	464/426	81.0	62.6	90.4
	7 sites	complete vaccination	147	24/12	123/116	96.5	64.3	99.7
PCV13 pneumonia	9 sites	at least one dose	877	344/167	533/491	84.7	75.7	90.4
	8 sites	complete vaccination	526	235/96	291/268	87.4	76.4	93.3
IPD severity								
PCV13 IPD deaths	6 sites	at least one dose	1464	21/14	1112/1044	84.7	55.7	94.7
	5 sites	complete vaccination	593	10/5	583/556	93.1	64.1	98.7

Outcome	Number of sites included	Exposure	Total	PCV13 IPD cases / vaccinated	NonPCV13 controls / vaccinated	PCV13 adjusted VE* (%)	LCI (%)	UCI (%)
PCV13 IPD admission to intensive care	7 sites	at least one dose	708	71/32	637/560	90.1	80.5	95.0
	7 sites	complete vaccination	281	43/14	238/200	94.3	82.3	98.2
IPD susceptibility to antimicrobials								
PCV13 penicillin non susceptible	6 sites	at least one dose	776	119/37	657/594	93.9	89.4	96.5
	6 sites	complete vaccination	365	77/14	288/253	96.6	91.8	98.6
PCV13 susceptible to penicillin	8 sites	at least one dose		176/73	829/754	92.4	87.5	95.3
	7 sites	complete vaccination	455	115/38	340/305	91.9	84.2	95.8
PCV13 erythromycin non susceptible	6 sites	at least one dose	649	62/26	587/532	92.1	83.9	96.1
	5 sites	complete vaccination	281	35/11	246/215	94.2	82.9	98.1
PCV13 susceptible to erythromycin	6 sites	at least one dose	775	188/56	587/532	95.2	91.9	97.2
	5 sites	complete vaccination	379	128/27	251/222	95.4	90.4	97.8
PCV13 non susceptible to cephalosporin	6 sites	at least one dose	703	81/22	622/560	95.4	90.7	97.7
	6 sites	complete vaccination	341	53/13	288/250	96.3	90.3	98.6
PCV13 susceptible to cephalosporin	7 sites	at least one dose	880	197/77	683/618	92.3	87.5	95.2
	6 sites	complete vaccination	401	131/32	280/247	93.8	87.6	96.9
Different schedules against PCV13 serotype IPD								
PCV13 serotypes	8 sites	1 dose <12 months	321	95/34	226/151	60.6	28.6	78.3
	9 sites	2 doses <12 months	587	111/51	476/399	76.1	60.1	85.6
	5 sites	3 doses 6-11 months	84	29/5	59/35	95.6	78.2	99.1
	8 sites	2+1 doses ≥12 months	1011	284/105	727/679	78.2	55.7	89.3
	8 sites	3+1 doses ≥12 months	416	235/47	181/127	89.7	81.6	94.3

* By site, age, year of notification and at least one underlying disease; IPD: invasive pneumococcal disease; LCI= lower confidence interval; UCI: upper confidence interval

In the analysis by time since vaccination, PCV13 effectiveness was 93.1% (87.8-96.1), 83.7% (70.2-91.0) and 85.1% (72.0-92.1) in the periods of <12, 12-23, ≥24 months after booster dose, respectively (Figure 3A). Vaccine effectiveness against PCV7 serotypes decreased from 98.5% (94.2-99.6) in the first 12 months after booster to 83.3% (32.5-95.9) ≥36 months since vaccination (p=0.025) (Figure 3B). PCV13 effectiveness against serotype 3 was 71.5% (34.6-87.6) <12 months since booster vaccination and 58.2% (-4.6 to 83.3) ≥24 months since vaccination (Figure 3C). The effectiveness against serotype 19A, was 94.4% (86.1-97.7) and 73.8% (30.3-90.1) <12 months and ≥24 months since booster vaccination, respectively (Figure 3D).

PCV10 effectiveness

A total of 857 (18%) IPD cases in children aged <5 years from four sites where PCV10 was used were eligible for this analysis. We finally included 636 (74%) IPD cases: 175 PCV10 cases, 150 serotype 19A IPD

and 311 nonPCV13 controls (Figure 4). Among the PCV10 serotypes, serotype 14 ranked first with 50 (29%) cases, followed by serotypes 1 (n=40, 23%), 19F (n=20, 11%) and 7F (n=19, 11%); the other serotypes represented 26% (n=46) of cases. Among nonPCV13 controls, the leading serotype was 10A (n=38, 12%), followed by serotype 15B/C (n=33, 11%), and 23B (n=31, 10%), with 27 other serotypes accounting for <10% of controls (Figure 4). PCV10 IPD cases were older and had lower proportions of cases presenting with meningitis than nonPCV13 controls (Table 5).

Table 5: Characteristics of PCV10 cases (n=175) and nonPCV13 controls (n=311) in the PCV10 analysis, 2011-2018, SplDnet multi-centre study

Characteristics	PCV10 IPD n=175	%	NonPCV13 controls n=311	%	p value
Number of cases					
Age group					<0.0001
• 2-23 months	93	53.1	223	71.7	
• 24-59 months	82	46.9	88	28.3	
Gender					1.0
• female	77	44.0	138	44.4	
• male	97	55.4	171	55.0	
• missing	1	0.6	2	0.6	
Year of notification					
• 2012	48	28.6	29	9.5	
• 2013	37	22.0	36	11.8	
• 2014	36	21.4	43	14.1	
• 2015	34	20.2	60	19.7	
• 2016	5	3.0	39	12.8	
• 2017	5	3.0	41	13.5	
• 2018	3	1.8	56	18.4	
Site					
• Czech Republic	21	12.0	23	7.4	
• Netherlands	18	10.3	185	59.5	
• Catalonia	108	61.7	44	14.1	
• Finland	28	16.0	59	19.0	
Outcome					0.134
• alive	164	93.7	223	71.7	
• dead	2	1.1	10	3.22	
• missing	9	5.1	78	25.1	
IPD cases by vaccination status					<0.0001
• at least one dose PCV10	27	15.4	231	74.3	
o completely vaccinated	19	10.9	138	44.4	
o partially vaccinated	3	1.7	86	27.7	
o uncertain schedule	5	2.9	7	2.25	
• unvaccinated	148	84.6	80	25.7	

IPD: invasive pneumococcal disease

The adjusted effectiveness of ≥ 1 PCV10 dose was 84.8% (69.4-92.5) against PCV10-serotype IPD, 88.0% (72.8-94.7) against PCV7-serotype IPD and 64.1% (-2.4 to 87.4) against PCV10non7 IPD (Table 6). PCV10 effectiveness of ≥ 1 dose was 27.2% (-187.6 to 81.6) and 85.3% (35.2-96.7) against the top serotypes 1 and 7F, and 32.5% (-28.3 to 64.5) and -14.4% (-526.5 to 79.1) against vaccine-related serotypes 19A and 6C, respectively.

Table 6: Vaccine effectiveness (VE) of at least one dose of PCV10 by outcome, 2011-2018, in 4 sites of the SpIDnet multi-centre study

Outcomes	Total	PCV10 IPD cases / vaccinated	NonPCV13 controls / vaccinated	PCV10 adjusted VE* (%)	LCI (%)	UCI (%)
Serotype groups						
PCV10 IPD	486	175/27	311/231	84.8	69.4	92.5
PCV7 IPD	427	116/15	311/231	88.0	72.8	94.7
PCV10non7 IPD	370	59/12	311/231	64.1	-2.4	87.4
PCV10 related serotypes**	379	73/51	306/217	-0.1	-142.0	58.6
Specific serotypes						
Serotype 1	351	40/7	311/231	27.2	-187.6	81.6
Serotype 7F	330	19/5	311/231	85.3	35.2	96.7
Serotype 19F	331	20/5	311/231	65.9	-36.4	91.5
Serotype 14	361	50/3	311/231	85.8	45.9	96.3
Serotype 19A	461	150/99	311/231	32.5	-28.3	64.5
Serotype 6C	311	17/14	294/217	-14.4	-526.5	79.1

* By site, age, and year of notification; ** exclude 19A ; IPD: invasive pneumococcal disease; LCI= lower confidence interval; UCI: upper confidence interval

DISCUSSION

Pooling IPD surveillance data from nine countries allowed measuring the serotype-specific vaccine effectiveness against IPD for the two PCVs used in Europe in 2011-18, with a high level of precision - that would be difficult with data from a single country. Our results indicate a high vaccine effectiveness for both PCVs against IPD due to the respective vaccine serotype groups, at around 84% for ≥ 1 dose.

PCV13 vaccine effectiveness was high against IPD due to individual vaccine serotypes, with point estimates ranging 85-98% for a complete schedule, except for serotype 3, for which the point estimate was much lower (65.5%). PCV13 effectiveness was high against IPD due to vaccine-related serotype 6C (94% for a complete schedule). PCV13 effectiveness was also high against individual clinical manifestations, disease severity and antimicrobial non-susceptible IPD. The results suggest that PCV13 effectiveness increased with the number of infant priming doses and for the 3+1 compared to the 2+1 schedule albeit with overlapping confidence intervals. The PCV13 results by time since vaccination indicate a waning immunity after the booster dose, which is more rapid for serotypes 3 and 19A. A longer follow-up with a larger sample size would be needed to assess the duration of protection offered by the different PCV13 schedules against specific serotypes, and to assess the public health importance of these findings.

In spite of combining multi-country level data, the number of IPD cases was insufficient to measure PCV10 effectiveness for the complete schedule or against specific outcomes. PCV10 effectiveness was high against IPD due to serotypes 14 and 7F and not significant against the other top vaccine serotypes (1 and 19F). We did not observe a significant PCV10 effectiveness against vaccine-related serotype 19A (33%, based on 249 19A cases) and serotype 6C (-14%, based on 31 6C cases).

Our overall results and the high effectiveness estimates against PCV13-serotype IPD support the results from other studies for schedules that include a booster in the second year of life ,regardless of the study design used.^{7 10 20-24}.

We observed a lower effectiveness against serotype 3, whose incidence has increased in countries of our network and in other countries with well-established PCV13 programmes and high vaccination coverage. A literature review of PCV13 effectiveness against serotype 3, which included earlier results of

our network, described an effectiveness ranging 20-80% for ≥ 1 PCV13 dose and 13-63% after the booster, with wide confidence intervals, which is consistent with our estimates.⁶ On the other hand, analysis of serotype 3 IPD cases in England and Wales estimated a serotype 3 vaccine effectiveness close to zero, with very wide confidence intervals.⁷ The authors suggested that the lack of vaccine effectiveness for serotype 3 IPD was unlikely to be due to differences in immunisation schedule because post-booster serotype 3 specific antibody concentrations are similar for 1+1, 2+1 and 3+1 PCV13 schedules.^{26 27} In England and Wales, there has been a substantial increase in IPD due to serotype 3 belonging to clade II after 2010 (reaching 50% of isolates in 2018) and two variants within the capsular operon have been identified within this clade which may have affected the capsular polysaccharide.²⁸ Whether these variants affect vaccine effectiveness by increasing capsular polysaccharide synthesis, for example, remains to be established. England was the second largest contributor to serotype 3 IPD data in our analysis (29% of serotype 3 cases); excluding England from our analysis increased the point effectiveness estimate from 65.5% (34.4-81.8) to 71.8% (41.0-86.5, data not shown). Repeated and larger studies would allow to determine whether PCV13 effectiveness against serotype 3 IPD differs by major circulating clades in Europe.

The study from England and Wales reported a lower PCV13 effectiveness against serotype 19A IPD (66.5% (44.6–79.8) for at least one dose and 84.2% (51.6–94.9) for the complete schedule) compared to our estimates (83.2% and 89.1%, respectively).⁷ Excluding England from our 19A analysis increased our estimates to 87.8% and 92.0%, respectively, because England was the main contributor with 38% of the 19A cases. We also observed a significant decline in PCV13 effectiveness against 19A after 12 months since booster; this trend was observed even after excluding England from analysis (from 91% <12 months to 69% ≥ 24 months since booster, $p=0.026$). Data from PCV13 sites of our network indicate that serotype 19A was the second most frequent cause of IPD in children in 2018 (9% in <5 year-olds), and its

incidence did not decrease further since 2014.^{29 30} Similar plateauing trends have been observed in non-SplDnet PCV13 countries as well. A genomic study identified a variant (sub-clade) of serotype 19A whose expansion contributed to the persistence of this serotype after PCV13 introduction in Ireland.³² Whether the remaining burden of serotype 19A in our network is related to waning of effectiveness or to clonal changes remains to be explored.

Our PCV10 effectiveness results are in line with the published studies from Canada and Brazil,^{20 38 39} and lower than those from observational studies in Finland.⁹ Our vaccine effectiveness estimates were remarkably similar for at least one dose for both PCV10 and PCV13 against IPD due to the respective vaccine serotype groups (84.8% versus 84.2%). However effectiveness against PCV10non7 serotypes, which are common to both vaccines, were higher for PCV13 compared to PCV10 (89% versus 65%), mainly because of lower PCV10 vaccine effectiveness against serotype 1.

We did not observed PCV10 effectiveness against vaccine-related serotypes 19A and 6C. Our PCV10 estimates against serotype 19A IPD were substantially lower and with wider confidence intervals than those reported by others studies using different study designs.^{9 20 38} The incidence of 19A IPD tended to rise in SplDnet sites using PCV10, as well as other countries using PCV10, such as Brazil,¹² Austria,³³ Canada,³⁵ and Belgium (where it re-emerged after a shift from PCV13 to PCV10 programme).^{8 36} These increases are worrisome because serotype 19A is highly invasive and has been associated with a high genetic diversity and high rates of antibiotic resistance.⁴⁰ We did not identify other studies measuring PCV10 effectiveness against serotype 6C IPD, but post-PCV10 increases in serotype 6C IPD incidence and/or carriage are described in other countries using PCV10 such as Austria,³³ Iceland,^{13 41} Belgium,⁴² and Brazil.⁴³

The observed PCV13 effectiveness against vaccine-related serotypes supported our decision to exclude them from the control group, to avoid underestimating vaccine effectiveness. This protection is restricted to serotypes 6A/6C and 7F/7A, for which cross-protection by vaccine-induced antibodies has been demonstrated,⁴⁴ but these serotypes represented a minority in our analysis. Serotype 23B predominated among vaccine-related serotypes, and the estimated PCV13 effectiveness against this serotype was higher than expected (Table 4). This value is probably significantly overestimated by the Broome method (Figure 2B),¹⁹ given the high carriage prevalence of this serotype post-PCV13 introduction and its low invasive potential (case-carrier ratio).⁴⁵

The main advantages of our study are the large sample size, using comprehensive surveillance data and harmonised surveillance methodology across a wide geographical area. The use of the indirect cohort method is based on the assumption that the control group comprising non-vaccine serotype IPD represents the general population in terms of vaccination uptake.¹⁸ In our study, this assumption is met because the proportion vaccinated in our control group was similar to vaccine coverage data provided by both PCV10 and PCV13 sites. However, this assumption may not hold if vaccination increases the risk of infection with non-vaccine pneumococcal serotypes among vaccinated children.¹⁹ Taking into account the high case-carrier ratio of PCV13 serotypes and the proportion of vaccine serotypes in IPD in our study, we may have overestimated the true vaccine effectiveness by <5%.¹⁹ In our study, the Broome method provides reliable effectiveness estimates, but these assumptions should be verified in following years. Another limitation related to Broome method is that it only provides an effectiveness estimate against vaccine-serotype IPD, which limits the use of data for wider analysis to aid vaccine policy decisions.

We included site as a fixed effect in the analysis assuming that the vaccine performs equally in all sites. In the two-stage analysis, the heterogeneity increased by adding additional years in the analysis,

although the point estimates in the primary analyses were comparable with those presented. However, we cannot exclude heterogeneity of vaccine effect due to different vaccine schedules and the timing of the individual doses. Finally, we have a proportion of cases with missing data. IPD cases with missing serotype information (12%) were older, less likely to be vaccinated or to present an underlying condition. If all IPD cases with missing serotypes were controls, the point estimate of PCV13 effectiveness against PCV13 IPD would have been overestimated by 5%. The proportion of cases with missing vaccination status was lower (3% overall), with no difference by age, case status or underlying conditions. Additionally, information on underlying conditions was not available for PCV10 analysis. However, this variable only marginally influenced the point estimate for PCV13 (<4%) and we do not expect this to be different for PCV10. **CONCLUSIONS**

Our results indicate a high effectiveness for both vaccines to protect against IPD caused by the respective vaccine serotypes in children age-group. We also noted a decrease in PCV13 effectiveness with time since booster vaccination. PCV13 provided individual protection against serotype 3 and vaccine-related serotype 6C IPD. PCV10 effectiveness was not significant against vaccine-related serotypes 19A and 6C. Several questions on conjugate vaccines effectiveness remain more than 10 years since their authorisation such as the potential waning protection for individual serotypes, or whether vaccines protect equally against all genetic variants within specific vaccine serotypes. Therefore, continuous, population-based surveillance for pneumococcal disease is crucial to monitor effectiveness of available vaccines. SpIDnet has demonstrated its value as a platform to provide evidence to support decision making on pneumococcal vaccination at the time of imminent deployment of a new generation of vaccines.

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423 CS was responsible for the study coordination, design of generic study protocols, collection of data from
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431

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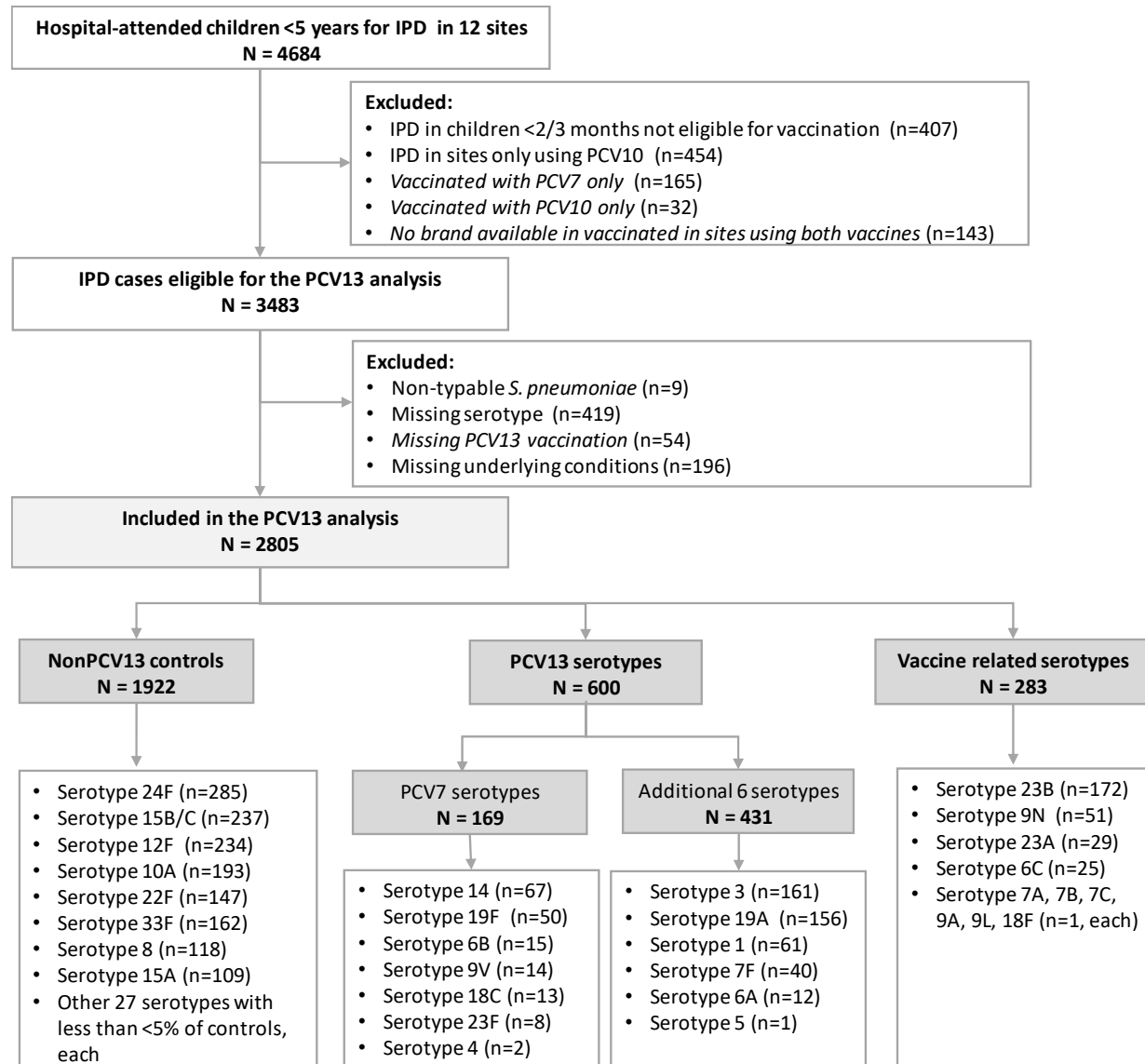
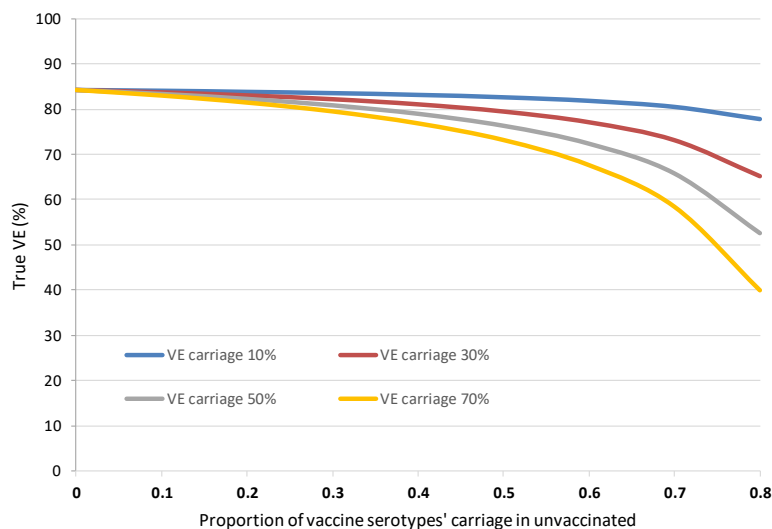


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A) VE against PCV13 IPD using Broome method = 84.2%



B) VE against 23B IPD using Broome method = 40.1%

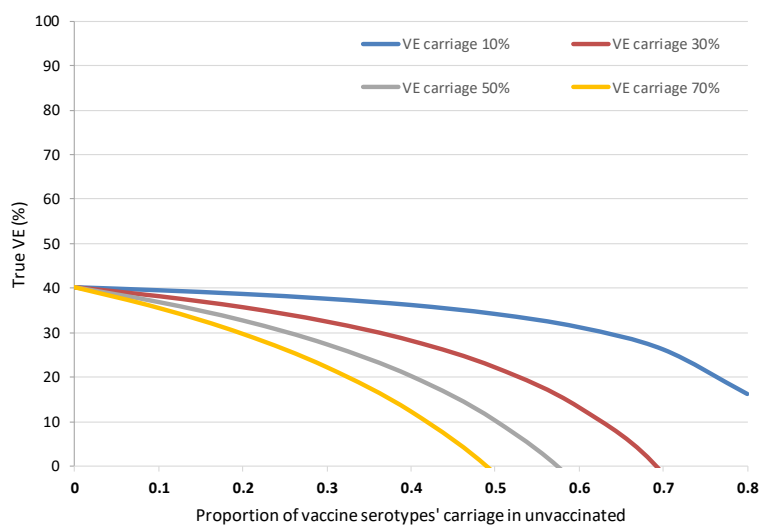


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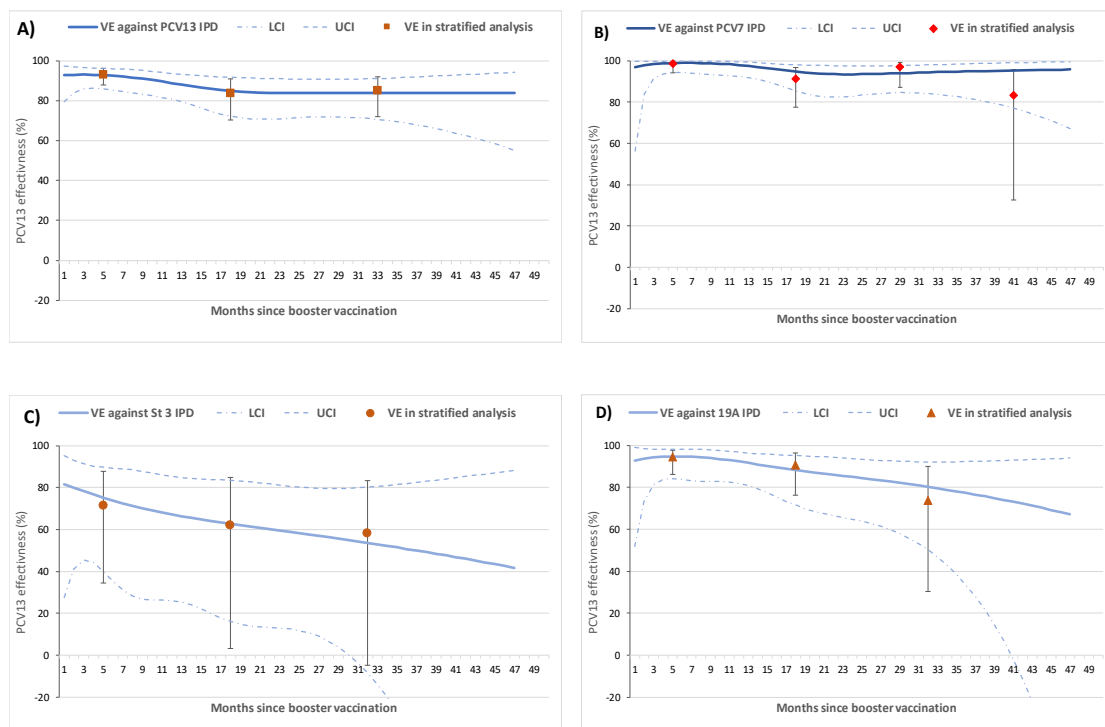


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