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Evaluating clinical effectiveness and impact of anti-pneumococcal vaccination in adults after universal childhood PCV13 implementation in Catalonia, 2017–2018

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ABSTRACT

Background: At present, because of indirect effects derived from routine childhood immunisation, clinical benefits vaccinating adults with the 23-valent pneumococcal polysaccharide vaccine (PPsV23) and/or the 13-valent pneumococcal conjugate vaccine (PCV13) are uncertain. This study investigated clinical effectiveness for both PPsV23/PCV13 in preventing pneumonia among Catalonian adults during an earlier 2-year period post-PCV13 free (publicly funded) approval for infants.

Methods: We conducted a Population-based cohort study involving 2,059,645 adults ≥ 50 years in Catalonia, Spain, who were followed between 01/01/2017–31/12/2018. Primary outcomes were hospitalisation from pneumococcal pneumonia (PP) or all-cause pneumonia (ACP) and main explanatory variable was PCV13/PPsV23 vaccination status. Cox regression models were used to estimate vaccination effectiveness adjusted by age/sex and underlying-risk conditions.

Results: Cohort members were followed for 3,958,528 person-years (32,328 PCV13-vaccinated, 1,532,186 PPsV23-vaccinated), observing 3592 PP (131 in PCV13-vaccinated vs 2476 in PPsV23-vaccinated) and 24,136 ACP (876 in PCV13-vaccinated vs 17,550 in PPsV23-vaccinated). Incidence rates (per 100,000 person-years) were 90.7 for PP (394.2 in PCV13-vaccinated vs 161.6 in PPsV23-vaccinated) and 609.7 for ACP (2636.3 in PCV13-vaccinated vs 1145.4 in PPsV23-vaccinated). The PCV13 was associated with an increased risk of PP (hazard ratio [HR]: 1.24; 95% CI: 1.00–1.52; p = 0.046) and ACP (HR: 1.38; 95% CI: 1.28–1.49; p < 0.001) whereas the PPsV23 did not alter the risk of PP (HR: 1.07; 95% CI: 0.98–1.18; p = 0.153) and slightly increased the risk of ACP (HR: 1.14; 95% CI: 1.10–1.18; p < 0.001). In supplementary analyses focused on at-risk individuals (i.e., elderly persons, immunocompromissing and other chronic illnesses) protective effects of vaccination did not emerge either.

Conclusions: Data does not support clinical benefits from pneumococcal vaccination (nor PCV13 neither PPsV23) against pneumonia among Catalonian middle-aged and older adults in the current era of universal PCV13 childhood immunisation in our setting. New extended valency PCVs are greatly needed.

Introduction

To date, despite successive formulations of anti-pneumococcal vaccines for adults and children during the past decades, infections caused by *Streptococcus pneumoniae*, mainly invasive pneumococcal disease (IPD) and pneumococcal pneumonia (PP) remain a major public health problem worldwide. Pneumococcal disease has a bimodal distribution, with a high burden among children under 5 years and adults over 50 years. In 2017, as well as 9,600 deaths by pneumococcal meningitis, pneumococcus caused approximately 659,000 low-respiratory infection deaths among people over 50 around the world.[1].

The existence of more than 90 pneumococcal serotypes (differing in their immunogenicity, virulence and epidemiological distribution in distinct geographical areas),[2] together with the observed phenomenon of serotype replacement after the introduc-

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tion of conjugate vaccines, has largely complicated the development of a fully effective anti-pneumococcal vaccination strategy.[1,3].

At present, apart from childhood immunisation, two antipneumococcal vaccines have been available for use in adults: the 23-valent pneumococcal polysaccharide vaccine (PPSV23, classically recommended for high-risk individuals and elderly people since the 1990s) and the 13-valent protein-polysaccharide conjugate vaccine (PCV13, initially marketed to replace PCV7 for childhood immunisation in 2010 and licensed for use in adults since 2012).[3] A major advantage for the PCV13 would be its theoretical higher immunogenicity, but, it has a lower serotype coverage than the PPSV23.[4].

Currently, pneumococcal vaccination (using distinct PPSV23/PCV13 schedules) for at-risk adults and elderly people is recommended in many countries.[1,3,5] However, diferent studies and meta-analyses estimating clinical effectiveness of PPSV23 and PCV13 in adults in recent years have revealed heterogeneous results,[6–12] and the cost-effectiveness of vaccinating adults with PCV13 and/or PPSV23 remains unclear (especially if we consider possible indirect effects derived from routine pediatric PCV13 use).[13–15].

In Catalonia, a region in Northeastern Spain with 7.6 million people, the PPSV23 has been recommended (and publicly funded) for all persons over 60 years (with or without risk conditions) and individuals under 60 years with at-risk conditions since 1999. The PCV13 (available for use in adults since 2012) is recommended for the same adult target population, although it is publicly funded only for high-risk individuals (basically immunocompromised patients). In children, a publicly funded vaccination programme offering a free PCV13 for all infants $\leq$ 2 years began in late 2016; before this date, the PCV7/PCV13 had been also used in children (without public funding, except for immunocompromised children).[16] PPSV23 and PCV13 effectiveness among adults was evaluated by our research team in a prior study performed during 2015–2016.[10] The present study is aimed to update information about the clinical effectiveness of adult vaccination after free PCV13 pediatric approval. Concretely, we assessed PPSV23 and PCV13 effectiveness in preventing hospitalised pneumonia (pneumococcal and all-cause), death from pneumonia and death from any cause among Catalonian people over 50 years-old throughout the 2017–2018 period (early 2-year period post-PCV13 free implementation in infants).

Methods

Design, setting and study population

This is a closed population-based retrospective cohort study involving 2,059,645 Catalonian middle-aged and older adults followed between 01/01/2017–31/12/2018. Cohort members were all persons 50 years or older (birth date before 01/01/1967) who were assigned to the 274 Primary Health Care Centers (PHCCs) managed by the Catalonian Health Institute (ICS, Institut Catala de la Salut) on January 1, 2017 (date of study start).

In the study region (Catalonia, Spain) there are 358 PCCs, of which 274 (76.5%) are managed by the ICS and 84 are managed by other providers. The analysed cohort (n = 2,059,645 persons $\geq$ 50 years) represented a 72.6% of the total 2,838,002 Catalonian inhabitants in this age strata according to census data in January 2017.[17] At the start of the study, antipneumococcal vaccination uptakes among at-risk/older adults were approximately 60% for the PPSV23 and 1% for the PCV13 (48% in children).[18,19].

For this report, cohort members were followed since the beginning of the study until the occurrence of any event, disenrollment from the PHCC, death, or until the end of the two-year follow-up (31/12/2018). The study was approved by the ethical committee of the Institution (ethic committee IDIAP Jordi Gol, file 20/065-PCV) and was conducted in accordance with the general principles for observational studies.[20] Considering population-based and non-interventional design, an individual consent for all study participants (n = 2,059,645) was exempt. Data analyses were anonymised and risk of identification was null.

Data sources

To establish baseline characteristics (vaccinations, comorbidities and underlying risk conditions) of the cohort at study start, as well as to identify vaccinations after study started, we used the information system for the development of research in primary care of Catalonia (SIDIAP),[21] which compiles administrative data and clinical information contained in the ICS's electronic PHCC medical records system and is usually used for epidemiological studies in the region. Quality criteria for clinical data of the SIDIAP research database has been reported elsewhere.[22].

To identify study events (hospitalisations from pneumococcal and all-cause pneumonia) that occurred in the study population throughout the study period, we used the national surveillance system for hospital discharge data (CMBD, Conjunto Mínimo Básico de Datos), which is maintained by the Spanish Ministry of Health and covers an estimated 99.5% of the total Spanish population (covered in the National Health Care System by compulsory health insurance).[23] In the present study we used CMBD hospital discharge codes, coded according to the International Classification of Diseases, 10th Revision (ICD-10), reported during 2017–2018 from 68 Catalonian hospitals.

Outcomes

Pneumococcal pneumonia (ICD-10 code J13), pneumonia by other microorganisms (codes J11.0, J12, J14-J17) and pneumonia by unidentified/unspecified microorganism (code J18) were defined on the basis of hospital discharge ICD-10 codes (any listed position) reported by the CMBD in hospitalisations occurring among cohort members from 01/01/2017 to 31/12/2018. Bacteremic PP was considered in those cases with ICD-10 code J13 plus A40.3 or B95.3. Death from any cause was considered according to administrative data (vital status), which is periodically updated in the SIDIAP data base. Death from pneumonia (case-fatality) was considered when the patient died within 30-day after pneumonia diagnosis.

Vaccination status

PPSV23 and PCV13 vaccination status were determined according to data registered in the PHCCs' electronic clinical records which contain specially designated fields for pneumococcal and influenza vaccinations (virtually all of them are administered at the PHCCs in the Spanish Health System). At baseline, cohort members were classified as PCV13 and/or PPSV23 vaccinated if they had received at least one dose of the vaccine before the study started. Throughout the study period, PCV13/PPSV23 vaccination status was a time-varying condition since some individuals received the vaccine after the study started. Subjects were considered to be vaccinated 14 days after vaccine administration. A subject was considered as unvaccinated when a vaccination was not recorded.

Covariates

Baseline covariates were age, sex, influenza vaccination in prior autumn, history of hospitalisation for pneumococcal disease or

pneumonia in the previous 2 years, history of chronic respiratory disease, chronic heart disease, chronic liver disease, diabetes mellitus, current smoking, alcoholism, and immunological situation. Immunocompromise was defined by the presence of any one of the following: asplenia, immunodeficiency/HIV-infection, severe chronic renal disease, bone marrow transplantation, cancer (solid organ or haematological neoplasia) and/or immunosuppressive medication. Definitions used to identify comorbidities/underlying conditions were listed in an appendix elsewhere.[10].

Statistical analyses

Incidence rates (IRs) were calculated as person-years, considering that the numerator was the number of events and the denominator was the sum of the persons-time contributed to each cohort member during the study period. Only a first episode of hospitalisation from pneumonia during the study period was considered and, therefore, the analyses do not include multiple events per person. To compare baseline characteristics of study subjects according to their PPSV23 and PCV13 vaccination status we used Chi-squared or Fisher's test as appropriate. Cox regression models for time-varying covariables were used to estimate hazard ratios (HRs) and evaluate the association between having received PPSV23/PCV13 and the time of the first outcome during the study period. The PPSV23 and the PCV13 vaccination status were considered time-varying conditions (e.g., subjects vaccinated after study started), whereas the other covariables were defined at study entry. All above mentioned covariables (i.e., age, sex, vaccinations' history, and presence of comorbidities/underlying risk conditions) were initially considered potential candidates for the calculation of multivariable Cox models. The method to select a subset of covariates to include in the final models was the purposeful selection. [24] The proportional hazard assumptions were assessed by adding the covariate by log-time interactions to the model. Both PCV13/

Table 1
Baseline characteristics of 2,059,645 cohort members according to their PCV13 and PPSV23 vaccination status before the study started (31/12/2016).

	PCV13 status[a]		**PPSV23 status**[b]	
	VACCINATED N=13,917 n (%)	**UNVACCINATED N=2,045,728 n (%)**	**VACCINATED N=798,548 n (%)**	**UNVACCINATED N=1,261,097 n (%)**
Age				
50-59 years	2720 (19.5)	738,216 (36.1)	31,953 (4.0)	708,983 (56.2)
60-69 years	3814 (27.4)	571,322 (27.9)	201,392 (25.2)	373,744 (29.6)
70-79 years	3994 (28.7)	409,285 (20.0)	297,072 (37.2)	116,207 (9.2)
≥80 years	3389 (24.4)	326,905 (16.0)	268,131 (33.6)	62,163 (4.9)
Sex				
men	7643 (54.9)	943,368 (46.1)	356,149 (44.6)	594,862 (47.2)
women	6274 (45.1)	1,102,360 (53.9)	442,399 (55.4)	666,235 (52.8)
Hospitalization history (previous 2 yrs)				
Invasive pneumococcal disease	50 (0.4)	682 (0.0)	478 (0.1)	254 (0.0)
Pneumococcal disease	186 (1.3)	2740 (0.1)	2055 (0.3)	871 (0.1)
Pneumococcal pneumonia	160 (1.1)	2321 (0.1)	1755 (0.2)	726 (0.1)
All cause pneumonia	746 (5.4)	16,021 (0.8)	12,294 (1.5)	4473 (0.4)
Vaccination history				
PPSV23 (at any time)	11,291 (81.1)	787,257 (38.5)	-	-
PCV13 (in previous 5 yrs)	-	-	11,291 (1.4)	2626 (0.2)
Flu vaccine (in prior autumn)	10,649 (76.5)	641,972 (31.4)	548,638 (68.7)	103,983 (8.2)
Risk level				
High risk	6779 (48.7)	196,668 (9.6)	122,606 (15.4)	80,841 (6.4)
At-risk	4763 (34.2)	796,229 (38.9)	374,802 (46.9)	426,190 (33.8)
Healthy	2375 (17.1)	1,052,831 (51.5)	301,140 (37.7)	754,066 (59.8)
Chronic respiratory disease	3798 (27.3)	196,898 (9.6)	134,005 (16.8)	66,691 (5.3)
Chronic heart disease	3349 (24.1)	216,333 (10.6)	156,673 (19.6)	63,009 (5.0)
Diabetes mellitus	4245 (30.5)	347,042 (17.0)	242,761 (30.4)	108,526 (8.6)
Chronic liver disease	986 (7.1)	39,937 (2.0)	19,208 (2.4)	21,715 (1.7)
Chronic renal disease	1612 (11.6)	20,924 (1.0)	17,657 (2.2)	4879 (0.4)
Alcoholism	505 (3.6)	64,513 (3.2)	23,047 (2.9)	41,971 (3.3)
Current smoking	1700 (12.2)	342,840 (16.8)	69,091 (8.7)	275,449 (21.8)
Asplenia	92 (0.7)	270 (0.0)	190 (0.0)	172 (0.0)
Primary immunodeficiency	124 (0.9)	674 (0.0)	459 (0.1)	339 (0.0)
HIV infection	820 (5.9)	3066 (0.1)	1950 (0.2)	1936 (0.2)
Bone marrow transplantation	1558 (11.2)	4597 (0.2)	3893 (0.5)	2262 (0.2)
Haematological neoplasia	395 (2.8)	6582 (0.3)	4051 (0.5)	2926 (0.2)
Solid neoplasia	1884 (13.5)	109,491 (5.4)	62,946 (7.9)	48,429 (3.8)
Immunosuppressive treatment	3308 (23.8)	78,997 (3.9)	50,964 (6.4)	31,341 (2.5)
Immunocompromise[c]	6779 (48.7)	196,668 (9.6)	122,606 (15.4)	80,841 (6.4)

NOTE: PCV13, 13 valent pneumococcal conjugate vaccine; PPSV23, 23 valent pneumococcal polysaccharide vaccine.

[a] Comparing PCV13 vaccinated vs unvaccinated, p-values (chi-squared test) were always statistically significant at $p < 0.001$, except for alcoholism ($p = 0.142$).

[b] Comparing PPSV23 vaccinated vs unvaccinated, p-values (chi-squared test) were always statistically significant at $p < 0.001$.

[c] Immunocompromise was a composite variable defined by the presence of any one of the following: cancer (solid organ or haematological neoplasia), chronic severe nephropathy (nephrotic syndrome, renal failure, dialysis or transplantation), anatomical or functional asplenia, immunodeficiency (including AIDS), and long-term corticosteroid therapy (20 mg/day of prednisone) or another immunosuppressive medication.

PPSV23, influenza vaccination status, history of prior pneumococcal disease and immunocompromising conditions were considered as epidemiologically relevant covariates, being included in all the final models. All models were compared by the partial likelihood ratio test and Akaike information criterion. Besides the main analysis including the total study cohort, we performed supplementary analyses by age subgroups, immunological status and four specific at-risk conditions (patients with chronic respiratory disease, chronic heart disease, diabetes mellitus and smokers). All results were expressed with 95% confidence intervals (CIs). Statistical significance was set at $p < 0.05$ (two-tailed). The analyses were performed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA).

Results

The 2,059,645 cohort members were observed for a total of 3,958,528 person-years, of which 1,532,186 were PPSV23 vaccinated and 33,228 were PCV13 vaccinated. Considering the PPSV23 status, 798,548 individuals had received PPSV23 before study start (contributing to the analyses with 1,500,833 person-years as PPSV23 vaccinated) and 41,745 individuals received PPSV23 later (contributing to the analyses with 51,392 person-years as PPSV23 unvaccinated and 31,353 person-years as PPSV23 vaccinated). As for the PCV13 status, 13,917 individuals had received PCV13 before study start (contributing to the analyses with 25,565 person-years as PCV13 vaccinated) and 7,769 individuals received PCV13 later (contributing to the analyses with 7,419 person-years as PCV13 unvaccinated and 7,664 person-years as PCV13 vaccinated). The vast majority (81.1%) of PCV13 vaccinated subjects had dual vaccination (PCV13 + PPSV23).

At baseline, mean age of cohort members was 66 years-old (standard deviation: 11.4), 951,011 (46.2%) men and 1,108,634 (53.8%) women. Considering comorbidities/underlying risk conditions, 351,287 (17.1%) cohort members had diabetes mellitus, 344,540 (16.7%) were smokers, 219,682 (10.7%) had chronic heart

Table 2
Incidence and risk of hospitalisation from pneumococcal and all-cause pneumonia in relation to PCV13 and PPSV23 vaccination status in the total study population (N = 2,059,645).

Parameter	Hospitalisation from pneumonia				
	Pneumococcal		Other microorganisms	Unknown ethiology	All-cause
	Bacteremic PP	All PP			
Number of events:					
All people	472	3592	4145	15399	24,136
PCV13 vaccinated	23	131	193	552	876
PCV13 unvaccinated	449	3461	4952	14847	23,260
PPSV23 vaccinated	273	2476	3656	11418	17,550
PPSV23 unvaccinated	199	1116	1489	3981	6586
Overall IR	11.9	60.7	130.0	389.0	609.7
(95% CI)	(10.8-13.1)	(85.2-96.5)	(122.1-138.3)	(365.3-413.9)	(572.5-648.7)
PCV13-vaccinated IR	69.2	394.2	580.8	1661.2	2636.3
(95% CI)	(43.9-103.8)	(332.7-466.7)	(504.1-668.5)	(1531.6-1800.7)	(2467.6-2815.6)
PCV13-unvaccinated IR	11.4	88.2	126.2	378.2	592.6
(95% CI)	(10.4-12.5)	(82.8-93.8)	(118.5-134.3)	(355.1-402.4)	(556.5-630.5)
PPSV23-vaccinated IR	17.8	161.6	238.6	745.2	1145.4
(95% CI)	(15.7-20.2)	(151.7-171.9)	(224.0-253.9)	(699.7-792.9)	(1075.5-1218.7)
PPSV23-unvaccinated IR	8.2	46.0	61.4	164.1	271.4
(95% CI)	(7.1-9.4)	(43.2-48.9)	(57.7-65.3)	(154.1-174.6)	(254.8-288.8)
Unadjusted HR					
For PCV13	4.65	3.63	4.20	4.09	4.04
(95% CI)	(2.90-7.45)	(2.99-4.40)	(3.61-4.89)	(3.74-4.46)	(3.76-4.34)
p value	<0.001	<0.001	<0.001	<0.001	<0.001
For PPSV23	2.02	3.40	3.75	4.40	4.09
(95% CI)	(1.69-2.43)	(3.16-3.64)	(3.53-3.98)	(4.25-4.57)	(3.97-4.20)
p value	<0.001	<0.001	<0.001	<0.001	<0.001
Age and sex-adjusted HR					
For PCV13	3.60	2.55	2.80	2.70	2.71
(95% CI)	(2.24-5.79)	(2.10-3.10)	(2.40-3.26)	(2.47-2.95)	(2.52-2.90)
p value	<0.001	<0.001	<0.001	<0.001	<0.001
For PPSV23	1.11	1.40	1.61	1.55	1.53
(95% CI)	(0.89-1.39)	(1.29-1.52)	(1.50-1.73)	(1.49-1.61)	(1.48-1.58)
p value	0.361	<0.001	<0.001	<0.001	<0.001
Multivariable-adjusted HR					
For PCV13	1.72	1.24	1.28	1.45	1.38
(95% CI)	(1.03-2.86)	(1.00-1.52)	(1.09-1.51)	(1.32-1.60)	(1.28-1.49)
p value	0.038	0.046	<0.001	<0.001	<0.001
For PPSV23	0.78	1.07	1.21	1.14	1.14
(95% CI)	(0.60-1.01)	(0.98-1.18)	(1.12-1.31)	(1.09-1.19)	(1.10-1.18)
p value	0.060	0.153	<0.001	<0.001	<0.001

NOTE: PP, pneumococcal pneumonia. IR, unadjusted incidence rate per 100,000 person-years. CI, confidence interval. PCV13, 13-valent pneumococcal conjugate vaccine. PPSV23, 23-valent pneumococcal polysaccharide vaccine.
HRs (hazard ratios) are for vaccinated subjects as compared with unvaccinated subjects and were adjusted, where appropriate, for age, sex, history of pneumococcal disease or pneumonia during the previous 24 months, presence of chronic pulmonary/respiratory disease, chronic heart disease, diabetes, chronic liver disease, alcoholism, current smoking, asplenia, immunodeficiency, HIV infection, chronic renal disease, bone marrow transplantation, cancer, immunosuppressive therapy, history of pneumococcal polysaccharide vaccination at any time and receipt or non receipt of influenza vaccine in prior autumn.

Table 3
Incidence and risk of death from pneumonia and death from any cause in relation to PCV13 and PPSV23 vaccination status in the total study population (N = 2,059,645).

Parameter	Death from pneumonia		Death from any cause
	Pneumococcal	All-cause	
Number of events:			
All people	272	2480	83,440
PCV13 vaccinated	8	66	1520
PCV13 unvaccinated	264	2414	81,920
PPSV23 vaccinated	211	1862	61,476
PPSV23 unvaccinated	61	618	21,964
Overall IR	6.9	62.6	2107.9
(95% CI)	(6.1-7.8)	(58.8-66.6)	(1979.3-2242.8)
PCV13-vaccinated IR	24.1	198.6	4574.5
(95% CI)	(10.4-47.5)	(155.9-252.2)	(4295.5-4867.3)
PCV13-unvaccinated IR	6.7	61.5	2087.0
(95% CI)	(5.9-7.6)	(57.7-65.4)	(1959.7-2220.5)
PPSV23-vaccinated IR	13.8	121.5	4012.3
(95% CI)	(12.0-15.9)	(114.1-129.3)	(3767.6-4269.1)
PPSV23-unvaccinated IR	2.5	25.5	905.2
(95% CI)	(1.9-3.3)	(23.5-27.6)	(850.0-963.1)
Unadjusted HR			
For PCV13	3.66	3.31	2.20
(95% CI)	(1.81-7.40)	(2.59-4.22)	(2.10-2.32)
p value	<0.001	<0.001	<0.001
For PPSV23	5.47	4.77	4.43
(95% CI)	(4.11-7.27)	(4.35-5.22)	(4.36-4.50)
p value	<0.001	<0.001	<0.001
Age and sex-adjusted HR			
For PCV13	2.39	2.24	1.58
(95% CI)	(1.18-4.84)	(1.75-2.86)	(1.50-1.66)
p value	0.015	<0.001	<0.001
For PPSV23	1.48	1.11	1.06
(95% CI)	(1.08-2.01)	(1.01-1.23)	(1.04-1.08)
p value	0.014	0.033	<0.001
Multivariable-adjusted HR			
For PCV13	1.43	1.24	1.03
(95% CI)	(0.68-3.00)	(0.96-1.60)	(0.98-1.09)
p value	0.344	0.105	0.275
For PPSV23	1.12	0.91	0.97
(95% CI)	(0.78-1.60)	(0.81-1.02)	(0.95-0.99)
p value	0.545	0.097	0.002

NOTE: IR, unadjusted incidence rate per 100,000 person-years. CI, confidence interval. PCV13, 13-valent pneumococcal conjugate vaccine. PPSV23, 23-valent pneumococcal polysaccharide vaccine.
HRs (hazard ratios) are for vaccinated subjects as compared with unvaccinated subjects and were adjusted, where appropriate, for age, sex, history of pneumococcal disease or pneumonia during the previous 24 months, presence of chronic pulmonary/respiratory disease, chronic heart disease, diabetes, chronic liver disease, alcoholism, current smoking, asplenia, immunodeficiency, HIV infection, chronic renal disease, bone marrow transplantation, cancer, immunosuppressive therapy, history of pneumococcal polysaccharide vaccination at any time and receipt or non receipt of influenza vaccine in prior autumn.

disease, 200,696 (9.7%) chronic respiratory disease, 118,352 (5.7%) cancer diagnosed in prior 5 years (6977 haematological neoplasia and 111,375 solid cancer), 65,018 (3.2%) alcoholism, 40,923 (2%) severe liver disease, 22,536 (1.1%) severe renal disease and 4684 (0.2%) immunodeficiency/HIV-infection.

Table 1 shows baseline characteristics of the 2,059,645 cohort members according to their PCV13 and PPSV23 vaccination status at study start. To summarize, vaccinated persons were older (especially PPSV23 vaccinated), had more comorbidities/underlying conditions (especially PCV13 vaccinated) and had greater influenza vaccine coverage than unvaccinated subjects.

During the two-year study period, 83,440 (4.1%) cohort members died and 51,175 (2.5%) moved or were lost subjects. A total of 24,136 cohort members suffered a first episode of hospitalisation for all-cause pneumonia, of which 3592 were pneumococcal pneumonia (472 bacteremic PP cases), 5145 were due to other microorganisms and 15,399 were due to unknown ethiology.

IRs (per 100,000 person-years) were 90.7 (95% CI: 85.2–96.5) for pneumococcal pneumonia (161.6 in PPSV23 vaccinated and 394.2 in PCV13 vaccinated), 130.0 (95% CI: 122.1–138.3) for pneumonia due to other microorganisms (238.6 in PPSV23 vaccinated and 580.8 in PCV13 vaccinated), 389.0 (95% CI: 365.3–413.9) for pneumonia due to unknown ethiology (745.2 in PPSV23 vaccinated and 1661.2 in PCV13 vaccinated) and 609.7 (95% CI: 572.5–648.7) for all-cause pneumonia (1145.4 in PPSV23 vaccinated and 2636.3 in PCV13 vaccinated).

Table 2 shows number of events, IRs, unadjusted, age and sex-adjusted and multivariable-adjusted risks of pneumococcal, other microorganisms, unknown ethiology and all-cause pneumonia in relation with PCV13 and PPSV23 vaccination status in the total study cohort. In the unadjusted analyses, as well as in the age and sex-adjusted analyses, both PCV13 and PPSV23 were associated with an increased risk for all analysed outcomes. In the multivariable analyses, having received the PPSV23 did not significantly alter the risk of overall pneumococcal pneumonia (HR: 1.07; 95% CI: 0.98–1.18; p = 0.153) and slightly increased the risk of all-cause pneumonia (HR: 1.14; 95% CI: 1.10–1.18; p < 0.001). Considering the PCV13, it appeared significantly associ-

Table 4
Stratified analyses on PPSV23 vaccination effectiveness according to age subgroups, immunological situation and distinct at-risk conditions.

	Age Strata		Immunological Status		At-risk conditions			
	50-59 years (N=740,936)	≥60 years (N=1,318,709)	Compromised (N=203,447)	Competent (N=1,856,198)	CRD (N=200,696)	CHD (N=219,682)	DM (N=351,287)	Smoking (N=344,540)
Bacteremic PP								
Number of events	98	374	126	346	150	105	133	123
PPSV23 multivariable HR	1.08	0.74	0.88	0.72	1.01	0.88	0.79	0.55
(95% CI)	(0.52-2.26)	(0.56-0.97)	(0.54-1.43)	(0.53-0.98)	(0.63-1.62)	(0.49-1.56)	(0.50-1.27)	(0.32-0.95)
p value	0.841	0.031	0.609	0.035	0.981	0.652	0.336	0.031
All PP								
Number of events	471	3121	877	2715	1169	885	1051	604
PPSV23 multivariable HR	1.49	1.05	1.26	0.98	1.18	1.32	1.02	1.08
(95% CI)	(1.09-2.03)	(0.95-1.16)	(1.04-1.52)	(0.88-1.10)	(0.98-1.42)	(1.07-1.64)	(0.85-1.22)	(0.86-1.35)
p value	0.012	0.375	0.019	0.747	0.078	0.011	0.830	0.500
All-cause pneumonia								
Number of events	2557	21,579	6265	17,871	7735	7000	7939	3558
PPSV23 multivariable HR	1.49	1.13	1.18	1.08	1.21	1.20	1.08	1.07
(95% CI)	(1.30-1.69)	(1.08-1.17)	(1.09-1.27)	(1.04-1.13)	(1.13-1.31)	(1.11-1.30)	(1.01-1.15)	(0.97-1.17)
p value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.031	0.177
Death from PP								
Number of events	18	254	71	201	66	82	80	35
PPSV23 multivariable HR	2.97	1.06	2.20	0.89	2.73	1.17	1.22	1.44
(95% CI)	(0.73-12.05)	(0.73-1.54)	(1.00-4.87)	(0.60-1.34)	(1.02-7.35)	(0.57-2.39)	(0.59-2.51)	(0.56-3.71)
p value	0.128	0.757	0.051	0.586	0.047	0.666	0.597	0.445
Death from pneumonia								
Number of events	124	2356	730	1750	681	845	821	311
PPSV23 multivariable HR	1.37	0.91	0.94	0.86	0.86	1.05	0.90	0.81
(95% CI)	(0.76-2.49)	(0.81-1.02)	(0.76-1.16)	(0.76-0.99)	(0.68-1.09)	(0.85-1.30)	(0.73-1.11)	(0.60-1.10)
p value	0.298	0.120	0.556	0.031	0.215	0.690	0.334	0.176
Death from any cause								
Number of events	5214	78,226	25,751	57,689	16,369	25,551	26,958	9045
PPSV23 multivariable HR	1.38	1.00	0.93	0.95	1.05	1.02	1.00	1.03
(95% CI)	(1.25-1.52)	(0.98-1.02)	(0.90-0.96)	(0.93-0.98)	(1.00-1.10)	(0.98-1.06)	(0.97-1.04)	(0.97-1.09)
p value	<0.001	0.980	<0.001	<0.001	0.055	0.363	0.956	0.371

Note: PP denotes pneumococcal pneumonia (any serotype). CRD: chronic respiratory disease; CHD: chronic heart disease; DM: diabetes mellitus. The HRs (hazard ratios) are for PPSV23 vaccinated subjects as compared with PPSV23 nonvaccinated and were adjusted, where appropriate, for age, sex, history of pneumococcal disease or pneumonia during the previous 24 months, presence of chronic pulmonary/respiratory disease, chronic heart disease, diabetes, chronic liver disease, alcoholism, current smoking, asplenia, immunodeficiency, HIV infection, chronic renal disease, bone marrow transplantation, cancer, immunosuppressive therapy, history of pneumococcal polysaccharide vaccination at any time and receipt or non receipt of influenza vaccine in prior autumn. CI denotes confidence interval.

ated with an increased risk for both pneumococcal pneumonia (HR: 1.24; 95% CI: 1.00–1.52; p = 0.046) and all-cause pneumonia (HR: 1.38; 95% CI: 1.28–1.49; p < 0.001).

In pneumococcal pneumonia, crude case-fatality rate was 7.6% [272/3592] overall, 6.1% [8/131] in PCV13 vaccinated and 8.5% [211/2476] in PPSV23 vaccinated (p = 0,343). With all-cause pneumonia, crude case-fatality rate was 10.3% [2480/24,147] overall, 7.5% [66/876] in PCV13 vaccinated and 10.6% [1852/17,550] in PPSV23 vaccinated (p = 0.004). Considering all-cause death, mortality rate was 2042 deaths per 100,000 person-years in the total study cohort, 4795 per 100,000 in PCV13 vaccinated and 3725 per 100,000 in PPSV23 vaccinated. After multivariable-adjustements, pneumococcal vaccination (neither PCV13 nor PPSV23) did not significantly alter the risk of death from pneumonia (pneumococcal and/or all-cause) while PPSV23 was associated with a little reduction risk of all-cause death (HR: 0.97; 95% CI: 0.95–0.99; p = 0.002) (Table 3).

Supplementary analyses focused on age subgroups (under/over 60 years), immunocompetent/immunocompromised subjects and specific at-risk comorbidity subgroups are shown in Table 4 (for the PPSV23) and Table 5 (for the PCV13). The PPSV23 was associated with a marginally significant reduction risk of bacteremic pneumococcal pneumonia in the age subgroup >=60 years (HR: 0.74; 95% CI: 0.56–0.97; p = 0.031) and immunocompetent persons (HR: 0.72; 95% CI: 0.53–0.98; p = 0.035), but no benefits emerged against all pneumococcal pneumonia and/or all-cause pneumonia. Considering the PCV13, clinical benefits did not emerge either. both PCV13 and PPSV23 were associated with an increased multivariable-adjusted risk of all-cause pneumonia in all analysed population subgroups (with HRs ranging between 1.07 and 1.49 for the PPSV23 and 1.11–1.41 for the PCV13).

Discussion

At present, after PCV13 introduction for infants, benefits from using PCV13 (and also PPSV23) in adults are uncertain.[13–15] The present study assessed clinical effectiveness and public health impact of PCV13/PPSV23 vaccinations in the general adult population over 50 years in Catalonia, Spain, throughout 2017–2018 (early two-year period after free PCV13 approval for infants). Data provided here updates data reported during 2015–2016 (before free PCV13 approval).[10].

As its main findings, pneumococcal vaccination has not emerged effective (neither PCV13 nor PPSV23) in preventing hospitalised pneumonia (pneumococcal or all-cause) and death from pneumonia in the total study cohort. In stratified analyses, the PPSV23 was associated with a marginally significant reduction risk of IPD (bacteremic PP) in the age subgroup over 60 years (where vaccine is recommended) and in immunocompetent persons. However, pneumococcal vaccination did not emerge effective (neither PPSV23 nor PCV13) against all pneumococcal pneumonia and/or all-cause pneumonia in specific at-risk population subgroups where vaccination is also recommended (i.e, immunocompromised subjects, chronic respiratory disease, heart disease or diabetes).

Considering pneumococcal pneumonia, our results are essentially similar to data observed during the 2015–2016 period and supports that vaccinating adults has not public health impact in reducing hospitalised pneumococcal pneumonia (all serotypes) in

Table 5
Stratified analyses on PCV13 vaccination effectiveness according to age subgroups, immunological situation and distinct at-risk conditions.

	Age Strata		Immunological Status		At-risk conditions			
	50-59 years (N=740,936)	≥60 years (N=1,318,709)	Compromised (N=203,447)	Competent (N=1,856,198)	CRD (N=200,696)	CHD (N=219,682)	DM (N=351,287)	Smoking (N=344,540)
Bacteremic PP								
Number of events	98	374	126	346	150	105	133	123
PCV13 multivariable HR	0.73	1.99	1.40	2.06	1.77	1.37	2.16	NA
(95% CI)	(0.16-3.39)	(1.16-3.39)	(0.71-2.75)	(0.97-4.40)	(0.87-3.62)	(0.53-3.59)	(0.98-4.77)	(-)
p value	0.687	0.012	0.326	0.061	0.117	0.518	0.056	-
All PP								
Number of events	471	3121	877	2715	1169	885	1051	604
PCV13 multivariable HR	1.20	1.22	1.09	1.39	1.12	1.09	1.08	0.75
(95% CI)	(0.68-2.12)	(0.97-1.52)	(0.83-1.45)	(1.03-1.88)	(0.83-1.51)	(0.74-1.58)	(0.75-1.54)	(0.40-1.41)
p value	0.528	0.084	0.537	0.031	0.474	0.672	0.688	0.366
All-cause pneumonia								
Number of events	2557	21,579	6265	17,871	7735	7000	7939	3558
PCV13 multivariable HR	1.11	1.40	1.30	1.41	1.32	1.33	1.30	1.16
(95% CI)	(0.86-1.43)	(1.29-1.51)	(1.18-1.44)	(1.26-1.58)	(1.18-1.47)	(1.17-1.51)	(1.15-1.47)	(0.92-1.46)
p value	0.415	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.212
Death from PP								
Number of events	18	254	71	201	66	82	80	35
PCV13 multivariable HR	1.93	1.28	1.57	0.83	0.95	2.13	0.35	2.66
(95% CI)	(0.26-14.57)	(0.56-2.95)	(0.63-3.89)	(0.21-3.38)	(0.27-3.33)	(0.76-5.92)	(0.05-2.70)	(0.49-14.34)
p value	0.523	0.561	0.334	0.799	0.933	0.149	0.312	0.255
Death from any cause								
Number of events	124	2356	730	1750	681	845	821	311
PCV13 multivariable HR	0.97	1.25	1.36	0.97	1.35	1.17	1.01	1.60
(95% CI)	(0.34-2.78)	(0.95-1.62)	(0.99-1.87)	(0.63-1.52)	(0.92-1.98)	(0.79-1.73)	(0.66-1.55)	(0.78-3.27)
p value	0.956	0.107	0.061	0.908	0.121	0.437	0.979	0.201
Death from any cause								
Number of events	5214	78,226	25,751	57,689	16,369	25,551	26,958	9045
PCV13 multivariable HR	1.00	1.03	0.93	1.10	0.98	0.99	1.00	0.91
(95% CI)	(0.81-1.23)	(0.97-1.09)	(0.86-0.99)	(1.02-1.19)	(0.89-1.07)	(0.91-1.08)	(0.92-1.08)	(0.76-1.08)
p value	0.999	0.314	0.031	0.018	0.637	0.864	0.933	0.283

Note: PP denotes pneumococcal pneumonia (any serotype). CRD: chronic respiratory disease; CHD: chronic heart disease; DM: diabetes mellitus. The HRs (hazard ratios) are for PCV13 vaccinated subjects as compared with PCV13 nonvaccinated and were adjusted, where appropriate, for age, sex, history of pneumococcal disease or pneumonia during the previous 24 months, presence of chronic pulmonary/respiratory disease, chronic heart disease, diabetes, chronic liver disease, alcoholism, current smoking, asplenia, immunodeficiency, HIV infection, chronic renal disease, bone marrow transplantation, cancer, immunosuppressive therapy, history of pneumococcal polysaccharide vaccination at any time and receipt or non receipt of influenza vaccine in prior autumn. NA denotes non available HR (zero cases in vaccinated).CI denotes confidence interval.

the current era of universal PCV13 infants' vaccination in our setting. In addition, data alerts about a posible increasing risk of all-cause pneumonia (non-vaccine pneumococcal serotypes, other microorganisms and/or unknown ethiology) among vaccinated subjects.

In this cohort study, crude IRs of hospitalisation from all-type pneumonia were largely higher in vaccinated than in nonvaccinated persons, reflecting the baseline excess risk of vaccinated subjects who were older and had more comorbidities/risk conditions than unvaccinated (especially for the PCV13). We try to resolve these baseline differences between vaccinated and unvaccinated subjects by multivariable analysis but, even after age/sex and underlying risk condition's adjustments, both PCV13 and PPSV23 remained significantly associated with an increased risk of all-cause pneumonia (both in the total study cohort as well as in stratified subgroups).

Opposite other recent studies in USA elderly people,[25,26] population benefits of PCV13 vaccination against all-type pneumonia have not emerged in the present study. We note that no adjustment method fully resolves confounding by indication in observational studies.[27] Regarding PCV13 (with very small vaccine coverage in our cohort since it was only funded for immunocompromised patients), caution is needed to interpret vaccines' effectiveness estimates (multivariable HRs) because it could simply reflect that the immunocompromised PCV13 vaccinated population had an enormously increased a priori risk of pneumococcal disease outcomes, and that PCV13 could not overcome this excess risk.

A lower risk for death from any cause was observed in certain analysis, such as the fully adjusted overall cohort and the immunocompetent adults (also oserved for death from all cause pneumonia). This data could simply reflect baseline risk differences between vaccinated and unvaccinated subjects, But It could also be related with the fact that pneumococcal pneumonia increases the risk for subsequent cardiac events and all-cause mortality.[28].

In this concern, there is insufficient evidence to draw conclusions on the impact of PCV13 or PPSV23 on mortality among older adults.[1].

During the past decades, likely related to differences in vaccination practices and smoking, the role of pneumococcus as a causative microorganism in pneumonia cases in developed countries has clearly declined (representing currently less than 10–15% of overall pneumonia cases in North America and Europe).[29,30] Therefore, the potential value of pneumococcal vaccination in reducing all-cause pneumonia has also decreased, and it would be relatively low at present. On this concern, pneumococcal

pneumonia represented 14.9% (3592/24,136) of overall pneumonia cases in the present study, supporting that the role of pneumococcus as causative pathogen of pneumonia has also declined in recent years in our setting (where pneumococcus represented near 40% of community-acquired pneumonia cases at the beginning of the present century).[31].

In the present study, data about pneumococcal serotypes was not available (since it is not reflected in the Spanish CMBD system) and, as consequent limitation, this study is not able to assess vaccination effectiveness against vaccine-type pneumococcal pneumonia (which would be the most specific outcome evaluating vaccines efficacy). It must be noted that the value of PCV13/PPSV23 vaccinating adults against all pneumococcal pneumonia (any serotype) has also decreased in recent years because indirect effects from routine PCV13 pediatric use.[32–37] In Spain, data from the National Surveillance Microbiology Laboratory of Pneumococcus has revealed that only a 29.7% of overall IPD cases (mostly bacteremic pneumococcal pneumonia) were caused by PCV13 serotypes during the 2017–2018 period.[33] In Catalonia, during the same period, PCV13 and PPSV23 serotypes represented 30.4% and 70.5%, respectively, of overall IPD cases (they were 40.4% and 73.6%during 2014–2015).[34].

In European PCV13 sites, several years after vaccine introduction, the incidence of IPD caused by PCV13 serotypes declined substantially in older adults (as indirect effect from childhood PCV13 vaccination) while the incidence of non-PCV13 serotypes increased 63%, resulting in a non-significant 9% reduction (95% CI: −4% to 19%) of IPD caused by all serotypes.[35] In the United States, where PCV13/PPSV23 uptakes among children and older adults are relatively high, only 4.6% of overall pneumonia cases hospitalised between October 2013 and September 2016 in people aged 18 years or more were caused by PCV13 serotypes (3.8–5.3% in patients aged 18–64 years depending on their risk status and 4.2% in people aged 65 years or older).[36].

The new generation of higher-valent PCVs (PCV15, PCV20 and future PCV24) have the potential to reduce a substantial proportion of pneumococcal disease cases among all age groups. However, considering the repeated serotype-replacement phenomenon observed after each PCV introduction, a new technology pneumococcal vaccine (with complete protection regardless of serotype) remains desirable.

Major strengths in this study are the largest size of the study cohort (which included more than 2 million adults over 50 years and represented almost 73% of the total Catalonian inhabitants in this age stratum), as well as the use of multivariable survival analysis methods to estimate accurately PCV13/PPSV23 effectiveness adjusted by major known underlying risk conditions. To our knowledge, this is the largest cohort study evaluating pneumococcal vaccination effectiveness in adults performed to date. Importantly, the study provides scarce population-based incidence data and it has been able to assess vaccination effectiveness against public health relevant outcomes (such as hospitalised all-type pneumococcal pneumonia, all-cause pneumonia and death from pneumonia) in distinct at-risk population subgroups of interest (e.g., chronic respiratory or cardiac disease, diabetics and smokers) where PPSV23/PCV13 effectiveness data is relatively rare in the literature.[38].

Major limitations in this study are related with its observational nature; mainly, the non-randomised vaccination, the small PCV13 coverage and the absence of serotype data. We assumed that hospital discharge coding was correct, but a validation diagnosis was not feasible considering study design and enormous size of the cohort. We did not consider time since vaccination in the analyses because of the vast majority of PPSV23 vaccinated had received the vaccine more than 5 years ago (since revaccination is not routinely recommended in aged > 65 years) and all PCV13 vaccinated had received the vaccine in previous 5 years (within 2012–2016).

We note that definition criteria of pneumococcal pneumonia vary between distinct studies, but we also note that the use of ICD diagnoses codes to define pneumococcal pneumonia, despite recognised limitations,[39] has been commonly used in many studies evaluating this issue. On this concern, we underline that all participating Catalonian hospitals basically apply similar diagnoses checklist and treatment for patients with a clinical suspicion of pneumonia (which is established on the basis of an acute respiratory illness, with evidence of a new infiltrate in a chest radiograph), being blood/sputum cultures and urinary antigen testing used as conventional diagnostic workup performed according to the attending physician.[40] As real world data study, vaccinations in this study were more frequently prescribed for persons with comorbidities/underlying risk conditions and, as above noted, may exists residual confounding in vaccines' effectiveness estimations despite multivariable adjustements. We recognise these limitations but, opposite to vaccine's efficacy that must be assessed by trials with controlled conditions, vaccination's effectiveness must be assessed by observational studies conducted in the real-world practice conditions, as in the present study, where vaccines are not homogeneously used. Caution is needed in extrapolating data to other geographical settings with distinct epidemiological conditions (i.e., different vaccines' use, vaccination uptakes among children and adults, prevalence of circulating serotypes, etc).

In conclusion, in this real world data study involving 2,059,645 Catalonian adults $\geq$ 50 years followed throughout 2017–2018, apart of a protective effect against IPD, clinical benefits of adults vaccination in preventing hospitalised all-type pneumococcal pneumonia or all-cause pneumonia have not emerged, neither for the PCV13 nor for the PPSV23. Our data supports that the current anti-pneumococcal vaccination strategy is insufficient to reduce pneumonia burden in at-risk and older adults in our setting.

At present, when PCV13 childhood immunisation is working and indirect effects have occurred (by reducing circulating PCV13 strains in the population), the potential value vaccinating adults with the PCV13 (but also with the PPSV23 which shares twelve common serotypes) has clearly decreased. Vaccinating adults using PCV13/PPSV23 could still provide clinical benefits in those settings where vaccine-type disease burden remains relatively high, but changes in adults vaccination strategies are necessary in settings where universal infants vaccination is working and, therefore, circulating vaccine-type serotypes are low.[1] In this way, CDC has recently approved new vaccinations' recommendations criteria for at-risk and older adults, supporting the use of the new generation of PCVs (PCV15 or better PCV20) in all age groups.[37].

Author contributions

AVC and OOG conceptualized and designed the study; AVC, CDC and ESG wrote and edited the manuscript; CDC, VTV, MFP and DRS assessed outcomes; CRC obtained data; ESG and AVR did statistical analyses; AVC coordinated the study. All authors have read and agreed to the final version of the manuscript.

Data availability

Interested authors might obtain SIDIAP data (previous ethics and scientific approval by the ethics and clinical research committee of the Primary Care Research Institute Jordi Gol (IDIAP Jordi Gol)).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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