BMC Infectious Diseases

RESEARCH

Open Access

Real world effectiveness of antipneumococcal vaccination against pneumonia in adults: a population-based cohort study, Catalonia, 2019

Cinta de Diego-Cabanes[1,3*], Verònica Torras-Vives[1,2], Angel Vila-Córcoles[1,3], Eva M. Satué-Gracia[1,2,3], M. José Forcadell-Peris[4], Frederic Gómez-Bertomeu[5], Leonardo de Esteban-Júlvez[6], Imma Hospital-Guardiola[1], Cruz M. Fuentes-Bellido[1], Anna Ribes-Alcover[7], Clara Rodriguez-Casado [8] and Olga Ochoa-Gondar[9]

Abstract

Background Despite recognised benefits against vaccine-type pneumococcal infections, limited and inconsistent evidence exists on the effectiveness of pneumococcal vaccination in preventing pneumococcal and all-cause pneumonia in adults. This study investigated clinical effectiveness of the 13-valent pneumococcal conjugate vaccine (PCV13) and the 23-valent pneumococcal polysaccharide vaccine (PPsV23) against hospitalised pneumococcal pneumonia (PP) and/or all-cause pneumonia (ACP) among middle-aged and older adults before COVID-19 pandemic started.

Methods Population-based cohort study involving 2,234,003 persons ≥ 50 years old in Catalonia, Spain, followed between 01/01/2019-31/12/2019. An Institutional Research database (SIDIAP-DB) was used to establish baseline characteristics of cohort members (demographics, underlying-risk conditions, vaccinations' history) and hospitalisations from PP/ACP were captured by hospital discharge codes (ICD10: J12-J18) in 68 referral Catalonian hospitals. Cox regression was used to evaluate the association between receipt of PCV13/PPsV23 and risk of PP/ACP.

Results Cohort members were followed for 2,194,200 person-years (23,494 PCV13-vaccinated and 783,465 PPsV23-vaccinated), observing 2319 hospitalised PP cases (110 in PCV13-vaccinated, 1558 in PPsV23-vaccinated) and 12,848 hospitalised-ACP cases (542 in PCV13-vaccinated, 9097 in PPsV23-vaccinated). Receipt PCV13 was associated with a greater risk of PP (multivariable-hazard ratio [MHR]: 1.83; 95%CI: 1.49–2.24) and ACP (MHR: 1.55; 95%CI: 1.42–1.70). Receipt PPsV23was also associated with increased risk of PP (MHR: 1.21; 95%CI: 1.10–1.36) and ACP (MHR: 1.24; 95%CI: 1.18–1.31) in the overall study cohort. Vaccination did not significantly alter the risk of death from PP/ACP. In sensitive analyses restricted to elderly (≥ 65 years old) and at-risk persons (immunocompromised, chronic respiratory/cardiac disease), PCV13 and/or PPsV23 did not emerge effective either.

*Correspondence:
Cinta de Diego-Cabanes
mcdiego.tgn.ics@gencat.cat

Full list of author information is available at the end of the article

Conclusion This study did not find evidence of the clinical effectiveness of PPsV23/PCV13 vaccination in preventing the outcomes measured at population-based level. At present, new extended-valency, PCVs (PCV15/PCV20/PCV21) have been marketed for using in adults and, logically, vaccines' effectiveness must be re-evaluated in the coming years.

Keywords Adults, Effectiveness, Pneumococcal conjugate vaccine, Pneumococcal polysaccharide vaccine, Pneumonia

Brief summary

Limited and inconsistent evidence exists on the effectiveness of PPSV23 and PCV13 in preventing pneumococcal and all-cause pneumonia in adults. In this population-based cohort study involving 2,234,003 Catalonian adults followed between 01/01/2019-31/12/2019, pneumococcal vaccination did not prove effective in preventing hospitalisation or death from pneumococcal and/or all cause pneumonia during the pre-COVID-19 year.

Background

Infections caused by *Streptococcus pneumoniae*, mainly invasive pneumococcal disease (IPD) and pneumococcal pneumonia (PP), remain a major public health problem worldwide. All-cause pneumonia (ACP), due to pneumococcus in many cases, is a global, regional and national leading cause of morbidity and mortality, especially among the elderly or those with risk conditions [1, 2].

During the past decades, various formulations of multivalent-serotype pneumococcal polysaccharide vaccines (PPSV) and protein-polysaccharide conjugate vaccines (PCVs) have been licensed for use in adults and children. Considering adults, the classical PPsV23 has been recommended to prevent IPD/PP among at-risk adults and elderly people since the 1990 s [3]. PCV13 (initially marketed to replace PCV7 in children) was approved for use in adults—particularly those at high risk—since the 2010 s [4, 5].

During this time, several randomised-controlled trials (RCTs) and observational studies have demonstrated vaccines' immunogenicity and clinical efficacy against vaccine-type IPD (which is a severe but relatively uncommon event) [6–8], but vaccination effectiveness and impact to prevent pneumonia (much more frequent event) among adults was uncertain (especially in adults with immunocompromising conditions, chronic illness and/or older age) [6, 9, 10].

Until now, pneumococcal vaccination using the classical PPsV23 in adults and, especially, PCV7/PCV13 in children has provided clear benefits decreasing rates of vaccine-type IPD in both children and adults (by direct effects but also by indirect effects derived from PCVs' childhood immunisation) [11–13]. However, at present, when routine PCVs childhood immunisation is working (and indirect effects are also probably occurring), clinical benefits and cost-effectiveness of anti-pneumococcal vaccination programmes in adults remain unclear [14, 15]. In fact, CDC's recommendations have changed across this time [5, 16, 17] and new extended-valency PCVs (PCV15/PCV20/PCV21) have been recently marketed to replace PCV13 use [18].

In this context, many countries maintain pneumococcal vaccination programmes using distinct vaccination schedules in children and adults, although current recommendations for pneumococcal vaccination in at-risk and older people are not homogeneous [18–20].

In Catalonia, a region in Northeastern Spain with 7.5 million inhabitants, the classical PPsV23 has been recommended and publicly funded for adults aged 18–64 years with certain at-risk conditions and for all elderly people (> 65 years) since the 2000s. PCVs (firstly PCV7 and later PCV13) were introduced for infants immunisation since their licensure in 2001 and 2010, respectively, being the PCV13 publicly funded for all infants < 2 years since 2016 [21]. In adults the PCV13 was publicly funded for immunocompromised subjects only, although being also prescribed (without public funding) by many clinicians for patients with other at-risk conditions (basically chronic pulmonary or cardiac disease and diabetes mellitus) [21].

Vaccination effectiveness of both PPsV23/PCV13 among Catalonian adults was assessed by our research team in a prior study conducted during 2017–2018 [22]. The present work is aimed to update information about PPsV23/PCV13 effectiveness among middle-aged and older adults before COVID-19 pandemic started. Concretely, we assessed real world effectiveness in practice for both PCV13/PPsV23 to prevent hospitalisation and death from pneumonia (PP and ACP) among the general population over 50 years throughout 01/01/2019-31/12/2019. In addition, we also explored vaccination effectiveness according to age strata, immunological status and presence of major comorbidities.

Of note, pneumococcal vaccine recommendations currently are different from what they were in 2019 before COVID-19. At present, the *Advisory Committee on Immunization Practices* (ACIP) of *Centers for Disease Control and Prevention* (CDC) recommends a single dose of the new PCV15, PCV20 or better PCV21 (all of which are not part of this study) [18]. In Catalonia, a single dose of the new PCV20 has replaced both PCV13 and PPsV23

in the current immunization schedule vaccinating adults since 2022.

Methods

Design, setting and study population

This is a population-based retrospective cohort study involving 2,234,003 Catalonian middle-aged and older adults followed between 01/01/2019-31/12/2019. Cohort members included all individuals aged 50 years or older (born before January 1, 1969) who were affiliated with any of the 274 Primary Care Centers (PCCs) managed by the Catalonian Health Institute (ICS, Institut Català de la Salut) across Catalonia on January 1, 2019 (the start date of this study). Characteristics of setting and study population have been extensively described elsewhere [23]. Cohort members were followed since the beginning of the study (Jan 1, 2019) until the occurrence of a first event (hospitalisation from PP or ACP), disenrollment from the PCC, death, or until the end of the study (Dec 31, 2019). The study protocol was approved by the ethics committee of the Institution (ethic committee of the *Institut d'Investigació Atenció Primària* [IDIAP] Jordi Gol, file P14/134; *Institut Catala de la Salut*; Barcelona). The present study was carried out in full compliance with the ethical principles established by the Declaration of Helsinki [23], including its later amendments. Furthermore, the study followed the guidelines for good research practices, specifically those concerning observational studies.

Data sources

We used the Information *System for the Development of Research in Primary Care in Catalonia* (SIDIAP database) [24], which compiles administrative data and clinical information from the ICS electronic medical records of PCCs, to determine baseline characteristics (vaccination history, comorbidities, and underlying risk conditions) of cohort members at study start, as well as to identify vaccinations, deaths, and/or disenrollment from PCCs after the study began. Hospitalisations from pneumonia (PP and/or ACP) that occurred among cohort members during the study period were identified using the national hospital discharge surveillance system (CMBD, *Conjunto Mínimo Básico de Datos*), maintained by the Spanish Ministry of Health and covering approximately 99.5% of the total Spanish population [25]. For this report, we used CMBD hospital discharge codes (any listed position), classified according to the International Classification of Diseases, 10th Revision (ICD-10), and reported from 68 Catalonian hospitals between January 1 and December 31, 2019. The methodology for linking CMBD and SIDIAP databases prior to analysis has been described elsewhere [26].

Outcomes

Hospitalisations for PP were defined according to ICD-10 hospital discharges coded as J13, whereas hospitalisations from ACP were defined for hospital discharges coded as J12-J18. Death from pneumonia (case-fatality) was considered when the patient died (any cause) within hospital stay. 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 [27]. Code J13 (equivalent to code 481 in the ICD-9) was applied in patients with x-ray confirmed pneumonia with *S. pneumoniae* isolated in blood/sputum cultures or positive urinary antigen test.

Vaccination status

PCV13 and PPsV23 vaccination status were considered according to data recorded in the SIDIAP database (which compiles data from the PCCs' electronic clinical records that contain specially designated fields for pneumococcal and influenza vaccinations in each individual). At study start, each cohort member was classified as PPsV23 and/or PCV13 vaccinated if they had received at least one dose of the vaccine before the study started. Throughout the study period, PPsV23/PCV13 status was a time-varying condition since some persons received the vaccine after study started. If a vaccination was not recorded, it was considered absent.

Covariables

Baseline covariables were age, sex, receipt of influenza vaccine in preceding autumn, history of chronic respiratory disease, chronic heart disease, chronic liver disease, diabetes mellitus, smoking, alcoholism and immunocompromising conditions (asplenia, immunodeficiency/HIV-infection, severe chronic renal disease, bone marrow transplantation, cancer [solid organ or haematological neoplasia] and/or immunosuppressive medication (see Appendix).

Data analyses

Statistical methods were previously described [22]. Briefly, we used Cox regression models for time-varying covariables to estimate hazard ratios (HRs) and evaluate the association between having received PCV13 or PPsV23 and the time of the first outcome during the study period. The PCV13 and the PPsV23 vaccination status were considered time-varying conditions (e.g., subjects vaccinated after the study started), whereas the other covariables were considered at study start. All above-mentioned covariables (i.e., age [continuous], sex,

influenza vaccine status and presence of underlying risk conditions), together with PCV13/PPsV23 status, were considered for the calculation and adjustment of the multivariable Cox models [28]. Besides the main analysis involving the total study cohort, we performed supplementary stratified analyses by age subgroups, high-risk (immunocompromised) individuals and those with specific at-risk conditions (chronic respiratory disease, heart disease and diabetes mellitus). 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 2,234,003 cohort members were followed for a total of 2,194,200 person-years, of which 783,466 person-years were for PPsV23-vaccinated individuals and 23,494 person-years for PCV13-vaccinated individuals. Across study period, 45,912 (2.06%) cohort members died, and 21,587 (0.97%) moved away or were lost to follow-up. Considering the PPsV23 status, 796,389 cohort members had received at least one dose of PPsV23 before study started (contributing to the analyses with 772,312 person-years as PPsV23-vaccinated) and 36,508 individuals received PPsV23 later (contributing to the analyses with 25,075 person-years as PPsV23-unvaccinated and 11,153 person-years as PPsV23-vaccinated). Regarding PCV13 status, 22,645 cohort members had received at least one dose of PCV13 before study started (contributing to the analyses with 21,775 person-years as PCV13-vaccinated) and 4316 individuals received PCV13 later (contributing to the analyses with 2431 person-years as PCV13-unvaccinated and 1719 person-years as PCV13-vaccinated). The vast majority (81.7%) of PCV13-vaccinated individuals had received both vaccines (PCV13 + PPSV23).

Baseline characteristics of the study cohort (mean age: 66 yrs [SD: 11.6]; 1,034,023 [46.3%] men and 1,199,980 [53.7%] women) according to PCV13/PPsV23 vaccination status at study start are shown in Table 1.

Across the study period, 2,319 hospitalised PP cases (110 in PCV13-vaccinated, 1,558 in PPsV23-vaccinated) and 12,848 ACP cases (542 in PCV13-vaccinated, 9,097 in PPsV23-vaccinated) were observed.

IRs (per 100,000 person-years) were 105.7 for PP (468.2 in PCV13-vaccinated vs. 198.9 in PPsV23-vaccinated) and 585.5 for ACP (2,307.0 in PCV13-vaccinated vs. 1,161.1 in PPsV23-vaccinated).

Globally, the observed case-fatality rates (CFRs) were 7.2% (166/2,319) for PP and 9.4% (1,204/12,848) for ACP. By vaccination status, CFRs for PP were 5.5% (6/110) in PCV13-vaccinated individuals vs. 7.2% (160/2,209) in PCV13-unvaccinated individuals ($p = 0.478$), and 7.9% (123/1,558) in PPsV23-vaccinated vs. 5.7% (43/761) in PPsV23-unvaccinated individuals ($p < 0.001$). CFRs for ACP were 10.7% (58/542) among PCV13-vaccinated individuals vs. 9.3% (1,146/12,306) in PCV13-unvaccinated individuals ($p = 0.278$), being 9.7% (882/9,097) in PPsV23-vaccinated individuals vs. 8.6% (322/3751) among PPsV23-unvaccinated individuals ($p = 0.050$).

Table 2 shows the absolute number of events (hospitalisations for PP/ACP and deaths from PP/ACP), as well as the unadjusted and multivariable-adjusted analyses on the risk of each event in relation to PCV13 and PPsV23 vaccination status in the total study cohort.

In the unadjusted analyses, both vaccines (especially PCV13) were associated with a greater risk for all events analysed, reflecting the baseline excess risk among vaccinated subjects.

After multivariable adjustment, a significant effectiveness of vaccination did not emerge either. Indeed, receipt PCV13 remained significantly associated with greater risk of PP (HR: 1.83; 95% CI: 1.49–2.24; $p < 0.001$) and ACP (HR: 1.55; 95% CI: 1.42–1.70; $p < 0.001$). Receipt of PPsV23 was also associated with a slightly increased risk of both PP (HR: 1.21; 95% CI: 1.10–1.36; $p = 0.001$) and ACP (HR: 1.24; 95% CI: 1.18–1.31; $p < 0.001$). Considering mortality, after multivariable adjustment, receipt of PPsV23 did not significantly alter the risk of death from PP (HR: 1.24; 95% CI: 0.53–2.91; $p = 0.625$) or from ACP (HR: 1.01; 95% CI: 0.86–1.18; $p = 0.946$). Receipt of PCV13 did not significantly alter the risk of death from PP (HR: 0.98; 95% CI: 0.64–1.49; $p = 0.928$) but was associated with a greater risk of death from ACP (HR: 1.91; 95% CI: 1.45–2.52; $p < 0.001$) (Table 2).

In separate analyses focusing on population subgroups for whom vaccination is strongly recommended -such as elderly people (i.e., aged ≥ 65 years), high-risk individuals (immunocompromised), and at-risk subgroups (chronic respiratory disease, chronic heart disease and/or diabetes mellitus), benefits from PCV13 or PPsV23 did not emerge either (Table 3).

Discussion

At present, more than 30 years after PPsV23 licensure and 10 years after PCV13 approval for adults, the clinical and public health benefits of using both vaccines to prevent pneumonia in at-risk and older adult populations remain uncertain [6, 9, 10, 14]. As main finding in this real-world data study, pneumococcal vaccination did not prove effective (neither PPsV23 nor PCV13) in preventing hospitalised pneumococcal pneumonia (PP), all-cause pneumonia (ACP) or death from PP/ACP in the overall study cohort. Stratified analyses focusing on elderly individuals, immunocompromised subjects and at-risk population subgroups did not reveal protective effects of vaccination either at population level.

Table 1 Baseline characteristics of cohort members (*N* = 2,234,003) according to their PCV13 and PPsV23 vaccination status before the study started (31/12/2018)

	PCV13 status[a]		PPsV23 status[b]	
	Vaccinated *N* = 22,645*n* (%)	**Unvaccinated *N* = 2,211,358*n* (%)**	**VaccinateD *N* = 796,389 *n* (%)**	**Unvaccinated *N* = 1,437,614 *n* (%)**
Age, 50–64 years	7508 (33.2)	1,128,965 (51.1)	73,203 (9.2)	1,063,270 (74.0)
65–79 years	10,088 (44.5)	734,514 (33.2)	441,655 (55.5)	302,947 (21.1)
≥ 80 years	5049 (22.3)	347,879 (15.7)	281,531 (35.4)	71,397 (5.0)
Sex, men	12,138 (53.6)	1,021,885 (46.2)	353,454 (44.4)	680,569 (47.3)
Women	10,507 (46.4)	1,189,473 (53.8)	442,935 (55.6)	757,045 (52.7)
Vaccination history	18,501 (81.7)	777,888 (35.2)	-	-
PPsV23 (at any time)	-	-	18,501 (2.3)	4144 (0.3)
PCV13 (in previous 5 yrs)	15,960 (70.5)	621,726 (28.1)	519,134 (65.2)	118,552 (8.2)
Flu vaccine (in prior autumn)				
Chronic respiratory disease	6998 (30.9)	240.736 (10.9)	152,623 (19.2)	95,111 (6.6)
Chronic heart disease	5867 (25.9)	269,388 (12.2)	184,976 (23.2)	90,279 (6.3)
Diabetes mellitus	6407 (28.3)	371,891 (16.8)	245,483 (30.8)	132,815 (9.2)
Chronic liver disease	1623 (7.2)	45,320 (2.0)	20,011 (2.5)	26,932 (2.9)
Chronic renal disease	2300 (10.2)	27,739 (1.3)	21,211 (2.7)	8828 (0.6)
Alcoholism	808 (3.6)	65,167 (2.9)	21,349 (2.7)	44,626 (3.1)
Current smoking	2911 (12.9)	382,605 (17.3)	68,608 (8.6)	316,908 (22.0)
Asplenia	141 (0.6)	323 (< 0.1)	245 (< 0.1)	219 (< 0.1)
Primary immunodeficiency	236 (1.0)	821 (< 0.1)	616 (0.1)	441 (< 0.1)
HIV infection	1341 (5.9)	3347 (0.2)	2420 (0.3)	2268 (0.2)
Haematological neoplasia	1143 (5.0)	4346 (0.2)	3024 (0.4)	2465 (0.2)
Solid neoplasia	2408 (10.6)	113,298 (5.1)	61,814 (7.8)	53,892 (3.7)
Immunosupresive treatment	3029 (13.4)	40,612 (1.8)	28,062 (3.5)	15,579 (1.1)
Immunocompromise[c]	8697 (38.4)	180,259 (8.2)	109,066 (13.7)	79,890 (5.6)

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

In this study, crude IRs for both PP/ACP events were largely greater among vaccinated than in unvaccinated individuals, reflecting the baseline excess risk of vaccinated subjects who were older and had more comorbidities than unvaccinated individuals (particularly among PCV13-vaccinated). We performed multivariable adjustments to account for these baseline differences between vaccinated and unvaccinated groups but, despite major underlying risk condition's adjustments, both PPsV23/PCV13 remained significantly associated with a greater risk of PP and ACP, both in the total study cohort as well as in age and at-risk stratified population subgroups. We note that no adjustment method fully resolves possible confounding by indication in observational studies and, consequently, a residual confounding in the final HRs estimations cannot be completely excluded [29]. Indeed, the most simplistic explanation for our negative findings would be that the baseline excess risk of vaccinated subjects (especially in the case of PCV13-vaccinated) was not entirely corrected in the final vaccines' effectiveness estimation, despite multivariable adjustments. Nevertheless, our data raise serious concerns about effectiveness and public health impact of the adult antipneumococcal vaccination program in Catalonian at the time of the study.

Over the past decade, PPsV23 and PCV13 have been recommended for at/high-risk adults and elderly people in many settings [3–5, 16–21]. However, several studies and meta-analyses have reported heterogeneous and not always favorable results [6, 8–10, 14, 22]. Indeed, apart from a demonstrated protective effect of vaccination against vaccine-type IPD/PP [6–10], results are less clear and heterogeneous regarding all pneumonia outcome [6, 14].

The last published Cochrane review found strong evidence of PPsV23 efficacy against IPD (VE: 74%; 95% CI: 55–86%), with estimated VE of 52% (95% CI: 39–63%) according to non-RCTs. This Cochrane review did not

Table 2 Incidence and risk of hospitalisation and death from Pneumococcal and all-cause pneumonia in relation to PCV13 and PPsV23 vaccination status in the total study population between 01/01/2019-31/12/2019 (*N* = 2,234,003)

Parameter	Hospitalization from pneumonia		Death from pneumonia	
	Pneumococcal	All-cause	Pneumococcal	All-cause
Number of events:				
All people	2319	12,848	166	1204
PCV13 vaccinated	110	542	6	58
PCV13 unvaccinated	2209	12,306	160	1146
PPsV23 vaccinated	1558	9097	123	882
PPsV23 unvaccinated	761	3751	43	322
Overall IR(95% CI)	105.7(99.3-112.5)	585.5(549.8–623.0)	7.6(6.5–8.9)	54.9(51.6–58.4)
PCV13-vaccinated IR(95% CI)	468.2(390.0-561.8)	2307.0(2110.9-2521.6)	25.5(9.4–55.6)	246.9(190.1–321.0)
PCV13-unvaccinated IR(95% CI)	101.8(95.6-108.3)	566.9(532.3-566.4)	7.4(6.3–8.7)	52.8(49.6–56.2)
PPsV23-vaccinated IR(95% CI)	198.9(186.8-211.6)	1161.1(1090.3-1235.4)	15.7(13.1–18.8)	112.6(105.4-120.3)
PPsV23-unvaccinated IR(95% CI)	53.9 (50.2–57.8)	265.9 (249.7-282.9)	3.0 (2.2-4.0)	22.8 (20.3–25.6)
Unadjusted HR				
For PCV13	4.63	4.09	3.48	4.70
(95% CI)	(3.82–5.61)	(3.75–4.46)	(1.54–7.87)	(3.61–6.12)
p value	< 0.001	< 0.001	0.003	< 0.001
For PPsV23	3.68	4.36	5.14	4.93
(95% CI)	(3.38–4.02)	(4.20–4.53)	(3.63–7.28)	(4.34–5.60)
p value	< 0.001	< 0.001	< 0.001	< 0.001
Age and sex-adjusted HR				
For PCV13	3.18	2.71	2.39	3.23
(95% CI)	(2.62–3.86)	(2.49–2.97)	(1.06–5.43)	(2.47–4.23)
p value	< 0.001	< 0.001	0.037	< 0.001
For PPsV23	1.62	1.72	1.27	1.27
(95% CI)	(1.46–1.80)	(1.65–1.80)	(0.87–1.85)	(1.10–1.46)
p value	< 0.001	< 0.001	0.213	0.001
Multivariable-adjusted HR				
For PCV13	1.83	1.55	0.98	1.91
(95% CI)	(1.49–2.24)	(1.42–1.70)	(0.64–1.49)	(1.45–2.52)
p value	< 0.001	< 0.001	0.928	< 0.001
For PPsV23	1.21	1.24	1.24	1.01
(95% CI)	(1.10–1.36)	(1.18–1.31)	(0.53–2.91)	(0.86–1.18)
p value	0.001	< 0.001	0.625	0.946

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 (continuous years), sex, influenza vaccination in preceding autumn, presence of chronic respiratory disease, chronic heart disease, diabetes, chronic liver disease, alcoholism, current smoking, asplenia, immunodeficiency, HIV infection, chronic renal disease, cancer, immunosuppressive therapy and receipt PCV13-PPsV23 at any time

find significant efficacy against all-cause pneumonia in high-income countries, either in the general population (VE: 29%; 95% CI: −12–55%) or in adults with chronic illness (VE: 7%; 95% CI: −19–27%) [6]. In the most recent meta-analysis on this concern, Farrar et al. concluded that available data suggested that both PPsV23 and PCV13 protect against vaccine-type IPD and vaccine-type PP, though heterogeneity across studies was wide [30]. Regarding all-cause pneumonia, some studies report modest benefits in reducing pneumonia-related hospitalisations [31], while others question the current clinical impact of these vaccines following widespread childhood immunisation [22]. Cost-effectiveness vaccinating adults with PPsV23 and/or PCV13 remains uncertain, depending on assumptions chosen (i.e., distinct levels of vaccines' coverage in children and adults, possibility of future serotype replacement after PCVs implementation, hypothetical level of vaccination effectiveness extrapolating by vaccines' efficacy, etc.) [15]. In this context, there is growing interest in newer-generation conjugate vaccines (PCV20/PCV21) due to their broader serotype coverage and potential immunological advantages [32].

In Catalonia, despite widespread pneumococcal vaccines' recommendations in children and adults [21], disease incidence and associated burden remains high [33, 34]. At present, the interpretation of adult vaccines'

Table 3 Stratified analyses on Pneumococcal vaccine's effectiveness (PCV13 and PPsV23) according to age subgroups, immunological situation and baseline comorbidities. NOTE: HR, hazard ratio. CI, confidence interval. PCV13, 13-valent Pneumococcal conjugate vaccine. PPsV23, 23-valent Pneumococcal polysaccharide vaccine

	Age group		**Immunological situation**		**Baseline conditions**		
	50-64 years*N*=1,136,476	**>=65 years*N*=1,097,530**	**Immunocompromised*N*=188,956**	**Immunocompetents*N*=2,045,047**	**Chronic respiratory diseases(*N*=247,734)**	**Chronic heart diseases(*N*=275,255)**	**Diabetes Mellitus(*N*=378,298)**
Pneumococcal pneumonia							
Number of events	511	1808	548	1771	969	721	689
Multivariable HR for PCV13	1.08	2.00	1,57	2.09	2.12	1.68	2.08
(95% CI)	(0.64-1.84)	(1.61-2.49)	(1.16-2.13)	(1.60-2.75)	(1.65-2.72)	(1.21-2.33)	(1.50-2.90)
p value	0.769	<0.001	0.003	<0.001	<0.001	0.002	<0.001
Multivariable HR for PPsV23	1.34	1.20	1.17	1.18	1.37	1.18	1.16
(95% CI)	(1.03-1.75)	(1.05-1.37)	(0.93-1.48)	(1.03-1.34)	(1.13-1.65)	(0.95-1.47)	(0.93-1.44)
p value	0.031	0.006	0.177	0.015	0.001	0.145	0.187
All-cause pneumonia							
Number of events	2396	10,452	3233	9615	4952	4426	4203
Multivariable HR for PCV13	1.41	1.53	1.24	1.89	1.58	1.47	1.48
(95% CI)	(1.14-1.77)	(1.39-1.70)	(1.08-1.42)	(1.68-2.13)	(1.40-1.78)	(1.28-1.69)	(1.27-1.71)
p value	0.002	<0.001	0.002	<0.001	<0.001	0.002	<0.001
Multivariable HR for PPsV23	1.50	1.22	1.15	1.22	1.32	1.18	1.19
(95% CI)	(1.33-1.69)	(1.15-1.29)	(1.04-1.27)	(1.16-1.30)	(1.21-1.44)	(0.95-1.47)	(1.09-1.31)
p value	<0.001	<0.001	0.005	<0.001	<0.001	0.145	<0.001

Table 3 (continued)

	Age group		Immunological situation		Baseline conditions		
	50-64 years*N*=1,136,476	**>=65 years*N*=1,097,530**	**Immunocompromised*N*=188,956**	**Immunocompetents*N*=2,045,047**	**Chronic respiratory diseases(*N*=247,734)**	**Chronic heart diseases(*N*=275,255)**	**Diabetes Mellitus(*N*=378,298)**
Death from PP							
Number of events	14	152	61	105	62	71	52
Multivariable HR for PCV13	1.72	1.17	0.56	1.94	1.92	1.23	1.02
(95% CI)	(0.16-18.87)	(0.47-2.95)	(0.13-2.42)	(1.26-2.97)	(0.73-5.02)	(0.37-4.08)	(0.22-4.73)
p value	0.659	0.738	0.438	0.002	0.183	0.738	0.977
Multivariable HR for PPsV23	0.59	0.99	1.25	0.99	1.03	1.28	0.80
(95% CI)	(0.12-2.82)	(0.64-1.54)	(0.62-2.51)	(0.82-1.20)	(0.47-2.24)	(0.59-2.76)	(0.37-1.71)
p value	0.509	0.962	0.529	0.914	0.946	0.528	0.561
Death from pneumonia							
Number of events	129	1,075	388	816	384	448	403
Multivariable HR for PCV13	2.19	1.86	1.73	1.94	2.24	1.93	2.06
(95% CI)	(0.91-5.27)	(1.38-2.49)	(1.20-2.50)	(1.26-2.97)	(1.54-3.26)	(1.27-2.92)	(1.34-3.16)
p value	0.082	<0.001	0.003	0.002	<0.001	0.002	0.001
Multivariable HR for PPsV23	1.12	1.00	0.94	0.99	0.93	1.18	0.97

Table 3 (continued)

	Age group		Immunological situation		Baseline conditions		
	50-64 years*N*=**1,136,476**	**>=65 years***N*=**1,097,530**	**Immunocompromised***N*=**188,956**	**Immunocompetents***N*=**2,045,047**	**Chronic respiratory diseases(*N*=247,734)**	**Chronic heart diseases(*N*=275,255)**	**Diabetes Mellitus(*N*=378,298)**
(95% CI)	(0.66-1.89)	(0.85-1.18)	(0.72-1.24)	(0.82-1.20)	(0.69-1.26)	(0.89-1.56)	(0.73-1.29)
p value	0.688	0.996	0.677	0.914	<0.001	0.262	0.843

NOTE: HRs (hazard ratios) are for vaccinated subjects as compared with unvaccinated subjects and were adjusted, where appropriate, for age (continuous years), sex, influenza vaccination in preceding autumn, presence of chronic respiratory disease, chronic heart disease, diabetes, chronic liver disease, alcoholism, current smoking, asplenia, immunodeficiency, HIV infection, chronic renal disease, cancer, immunosuppressive therapy and receipt PCV13-PPsV23

effectiveness is increasingly complex due to indirect effects from paediatric vaccination and serotype replacement [35]. Indeed, the indirect effects of childhood vaccination have been pointed as key to understanding the reduced effectiveness of PCV13 and PPsV23 in adults today [36, 37].

From a public health point of view, recognizing a demonstrated protective effect of PPsV23/PCV13 against vaccine-type IPD (which is a relatively infrequent event that is not evaluated in the present study, our real-world data alerts about the possibility of a non significant protective effect to reduce hospitalisations from PP/ACP in the adult population at the time of the study. Of note, according to most meta-analyses, PPsV23 vaccination effectiveness against pneumonia has never clearly been demonstrated in older adults, immunocompromised subjects and persons with chronic illnesses [6, 8–10, 14].

We underline the importance of RCT data assessing vaccine's efficacy, but also note the absence of relevant RCT data (i.e., clinical effectiveness, not simply immunogenicity data) during the last ten years in relation with pneumococcal vaccines in adults [16–18]. Indeed, since the CAPITA RCT (that evaluated PCV13 vs. placebo among elderly people in the Netherlands across 2008–2012) [7], no RCT has been published evaluating clinical efficacy/effectiveness of pneumococcal vaccines in adults. Thus, considering documented changes in pneumococcal disease epidemiology across this time [13, 37, 38], large cohort studies conducted in the real-world practice conditions (as the present study) are necessary to inform about clinical effectiveness and real impact of current antipneumococcal vaccination programmes in adults [39].

Major strengths in this study are the large size and representativity of the studied cohort (which included more than two million people over 50 years (almost a 75% of the overall Catalonian inhabitants in this age stratum) [40] and the use of survival analysis methods to estimate the association between PPsV23/PCV13 vaccination and the risk of clinically important and public health relevant outcomes such as hospitalisation and death from PP/ACP. While it is not a RCT, the largest sample size together with the adjustment of major potential confounder variables (e.g., age, influenza vaccine status and presence of main comorbidities/risk conditions) in the multivariable analyses, may provide an acceptable basis to estimate PCV13/PPsV23 effectiveness in Catalonian adults during the preceding year before COVID-19 pandemic started and new PCVs were licensed. Of note, a key gap in the literature is the absence of studies assessing PPsV23 and PCV13 vaccine effectiveness in the same adult population [41].

The main limitations in this study are related to its observational nature (i.e., non-randomised vaccination),

scarce PCV13 coverage, and the absence of serotype data (which is not reflected in the Spanish hospital discharge system). Despite the enormous cohort size, the study was largely underpowered to accurately assess PCV13 effectiveness due to its very low vaccine coverage (approximately 1%) in the studied cohort.

We also underline potential limitations inherently related to the use of secondary data sources in this research (records in SIDIAP and CMBD databases) and note that we do not know how much influence the use of these secondary data in the negative results observed in the present study. The ICD hospital discharge codes to identify pneumonia cases, despite recognized limitations [42], have been commonly used in many epidemiological studies on this concern [2]. All-cause pneumonia outcome could conduct to misclassification in some cases, but we also note that it has been considered an acceptable outcome in most meta-analyses published evaluating pneumococcal vaccines' effectiveness [6, 8–10, 14]. This study is not exempt from possible misclassification bias related to criteria used to define vaccination status. We underline that we used a feasible/operational criteria based on the reception of at least one dose of PPsV23 at any time or a dose of PCV13 (always within the last five years) to classify a person as PPsV23 or PCV13 vaccinated. However, we note that this could not adequately reflect a complete immunisation schedule in some individuals (depending on age, risk factors and time elapsed since prime dose).

This study was unable to assess vaccine-type IPD/PP (which would be the most specific outcome evaluating vaccine efficacy) due to the lack of serotype data. Nevertheless, it is largely able to provide uncommon population-based incidence data and evaluate other clinically important outcomes such as hospitalisation and death from all-type pneumococcal and all-cause pneumonia, which are especially relevant since a public health point of view. Our data will be also important to establish future comparisons with population-based incidence data for hospitalised PP/ACP that are occurring today (where new PCVs have been introduced and are working) [32]. In 2019, the most prevalent invasive pneumococcal serotypes among adults in Catalonia were 8, 3 and 12 F, partially covered by existing vaccines: The PCV13 covered 30.2% of identified serotypes in 20–64-year-olds and 26.5% in ≥65-years, while PCV20 coverage was 79.6% and 64.8%, respectively [34]. Although these data refer to invasive pneumococcal disease (IPD), they provide a useful snapshot of circulating serotypes in Catalonian adults at the time of the study [34]. We underline that this study was conducted in a single geographical region (Catalonia) with a relatively low incidence of pneumococcal infections (11 IPD cases per 100,000 inhabitants/year during 2017–2018) [43] and, logically, vaccine effectiveness may vary in other settings with other epidemiological circumstances.

Conclusion

In conclusion, neither PPsV23 nor PCV13 were associated with a reduced risk of hospitalisation or death from all-type pneumococcal or all-cause pneumonia in this large, population-based cohort of adults over 50 years in Catalonia during 2019 (prior to the COVID-19 pandemic). Nevertheless caution is needed before interpreting and generalising the results, due to the inherent limitations of the observational and non-randomised design of this study.

At present, new extended-valent PCVs (PCV15/PCV20/PCV21) have been marketed for using in adults and, logically, vaccines' effectiveness must be re-evaluated in the coming years.

Abbreviations

ACIP	Advisory Committee on Immunization Practices
ACP	All-cause pneumonia
CDC	Centers for Disease Control and Prevention
CFR	Case-fatality rate
CI	Confidence interval
CMBD	Conjunto Mínimo Básico de Datos (national surveillance system for hospital discharge data)
COVID-19	Disease by SARS_COV_2 viruses
EPIVAC	Effectiveness of Pneumococcal and Influenza Vaccination Adults in Catalonia
ICD-10	International Classification of Diseases, 10th Revision
ICS	*Institut Català de la Salut* (Catalonian Health Institute)
IPD	Invasive pneumococcal disease
IR	Incidence rate
HR	Hazard ratio
PCC	Primary care center
PCV	Pneumococcal conjugate vaccine
PPsV	Pneumococcal polysaccharide vaccine
PP	Pneumococcal pneumonia
RCT	Randomised controlled trial
SIDIAP	Information system for the development of research in primary care of Catalonia

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-11596-w.

Supplementary Material 1

Acknowledgements

The authors would like to thank the Instituto de Salud Carlos III (Madrid), file grant PI 20/01223, the IDIAP Jordi Gol Foundation (Barcelona), and the Hospital Joan XXIII Foundation (Tarragona) for their support in the publication of this paper. The authors also extend their gratitude to Angel Vila-Rovira as well as to all the EPIVAC group collaborators, for the assistance in the preparation of this manuscript. This work was supported by the Industrial Doctorates Plan of the Department of Research and Universities of the Government of Catalonia.

Clinical trial number

not applicable.

Authors' contributions

CDC, VTV and AVC wrote and edited the manuscript; CRC obtained data; CDC, VTV, FGB, LEJ, MJFP, IHG, CFB and ARA assessed outcomes; ESG did statistical

analyses; AVC and OOG coordinated the study. The two first listed authors contributed similarly to this manuscript. All authors have read and agreed to the final version of the manuscript.

Funding
This work was supported by the Industrial Doctorate Program of the Agency for Administration of University and Research Grants (AGAUR), Government of Catalonia (Agència de Gestió d'Ajuts Universitaris i de Recerca, Generalitat de Catalunya), grant number 2024 DI 00073.

Data availability
Data have been obtained from the Catalonian Health Institute Information System for the Development of Research in Primary Care (SIDIAP). Interested authors might obtain SIDIAP data (previous ethics and scientific approval by the ethics and clinical research committee of the Institut d'Investigació Atenció Primària (IDIAP) Jordi Gol, Barcelona) addressing purposes to the Institution.

Declarations

Ethics approval and consent to participate
All methods were performed in accordance with relevant guidelines and regulations. The study was approved by the Ethics Committee of the Institution (*Institut d'Investigació Atenció Primària* [IDIAP] Jordi Gol, file P14/134; *Institut Català de la Salut*; Barcelona) and was conducted in accordance with the general principles for observational studies. The need for informed consent was waived by the Ethics Committee of the Institution due to the nature of the data (pseudonymised) and according to the European General Regulation for Data Protection, RGDP, article 6.e, 9.2.j and 89. The present study was carried out in full compliance with the ethical principles established by the Declaration of Helsinki, including its later amendments. Furthermore, the study followed the guidelines for good research practices, specifically those concerning observational studies.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Institut Català de la Salut. Primary Health Care Service Camp de Tarragona, Institut Català de la Salut, Tarragona, Spain
[2]Universitat Rovira I Virgili, Programa Biomedicina, Tarragona, Spain
[3]Unitat de Suport a la Recerca of Tarragona, Fundació Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol), Tarragona, Spain
[4]Institut Català de la Salut. Primary Health Care Service Terres de l'Ebre, Institut Català de la Salut, Amposta, Spain
[5]Laboratori Clínic ICS Camp de Tarragona I Terres de l'Ebre, Institut Català de la Salut, Tarragona, Spain
[6]Pneumology Department, Hospital Universitari Joan XXIII, Institut Català de la Salut, Tarragona, Spain
[7]SEGIV Vacunes Tarragona/Terres de l'Ebre, Institut Català de la Salut, Tarragona, Spain
[8]Fundació Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol), Barcelona, Spain
[9]Gerència d'Atenció Primària i a la Comunitat. Àmbit Camp de Tarragona, Institut Català de la Salut. Primary Health Care Service Camp de Tarragona, Institut Català de la Salut, Tarragona, Spain

Received: 4 June 2025 / Accepted: 28 August 2025
Published online: 21 October 2025

References

1. Safiri S, Mahmoodpoor A, Kolahi AA, Nejadghaderi SA, Sullman MJM, Mansournia MA, et al. Global burden of lower respiratory infections during the last three decades. Front Public Health. 2023;10:1028525.
2. Torres A, Cillóniz C, Blasi F, Chalmers JD, Gaillat J, Dartois N, et al. Burden of pneumococcal community-acquired pneumonia in adults across Europe: a literature review. Respir Med. 2018;137:6–13. https://doi.org/10.1016/j.rmed.2018.02.007.
3. Centers for Disease Control and Prevention. Prevention of pneumococcal disease: recommendations of the advisory committee on immunization practices (ACIP). MMWR Morb Mortal Wkly Rep. 1997;46:1–24.
4. Centers for Disease Control and Prevention. Use of 13-valent Pneumococcal conjugate vaccine and 23-valent Pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the advisory committee on immunization practices (ACIP). MMWR Morb Mortal Wkly Rep. 2012;61:816–9.
5. Centers for Disease Control and Prevention. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥ 65 years: recommendations of the advisory committee on immunization practices (ACIP). MMWR Morb Mortal Wkly Rep. 2014;63:822–5.
6. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing Pneumococcal infections in adults (review). Cochrane Database Syst Rev. 2013;1:CD000422.
7. Bonten MJ, Huijts SM, Bolkenbaas M, Webber C, Patterson S, Gault S, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med. 2015;372(12):1114–25. https://doi.org/10.1056/NEJMoa1408544.
8. Falkenhorst G, Remschmidt C, Harder T, Hummers-Pradier E, Wichmann O, Bogdan C. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine (PPV23) against pneumococcal disease in the elderly: systematic review and meta-analysis. PLoS One. 2017;12(1):e0169368. https://doi.org/10.1371/journal.pone.0169368.
9. Schiffner-Rohe J, Witt A, Hemmerling J, von Eiff C, Leverkus FW. Efficacy of PPV23 in preventing pneumococcal pneumonia in adults at increased risk–a systematic review and meta-analysis. PLoS One. 2016;11(1):e0146338. https://doi.org/10.1371/journal.pone.0146338.
10. Tin Tin Htar M, Stuurman AL, Ferreira G, Alicino C, Bollaerts K, Paganino C, et al. Effectiveness of pneumococcal vaccines in preventing pneumonia in adults, a systematic review and meta-analyses of observational studies. PLoS One. 2017;12(5):e0177985. https://doi.org/10.1371/journal.pone.0177985.
11. Càmara J, Marimón JM, Cercenado E, Larrosa N, Quesada MD, Fontanals D, et al. Decrease of invasive Pneumococcal disease (IPD) in adults after introduction of Pneumococcal 13-valent conjugate vaccine in Spain. PLoS ONE. 2017;12(4):e0175224. https://doi.org/10.1371/journal.pone.0175224.
12. Waight PA, Andrews NJ, Ladhani SN, Sheppard CL, Slack MP, Miller E. Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: an observational cohort study. Lancet Infect Dis. 2015;15(5):535–43.
13. Hanquet G, Krizova P, Valentiner-Branth P, Ladhani SN, Nuorti JP, Lepoutre A, et al. Effect of childhood pneumococcal conjugate vaccination on invasive disease in older adults of 10 European countries: implications for adult vaccination. Thorax. 2019;74(5):473–82. https://doi.org/10.1136/thoraxjnl-2018-211767.
14. Berild JD, Winje BA, Vestrheim DF, Slotved HC, Valentiner-Branth P, Roth A, et al. Systematic review of studies published between 2016 and 2019 on the effectiveness and efficacy of pneumococcal vaccination on pneumonia and invasive pneumococcal disease in an elderly population. Pathogens. 2020;9(4):259. https://doi.org/10.3390/pathogens9040259.
15. Treskova M, Scholz SM, Kuhlmann A. Cost effectiveness of elderly pneumococcal vaccination in presence of higher-valent pneumococcal conjugate childhood vaccination: systematic literature review with focus on methods and assumptions. Pharmacoeconomics. 2019;37(9):1093–127. https://doi.org/10.1007/s40273-019-00805-5.
16. Matanock A, Lee G, Gierke R, Kobayashi M, Leidner A, Pilishvili T. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥ 65 years: updated recommendations of the advisory committee on immunization practices. MMWR Morb Mortal Wkly Rep. 2019;68(46):1069–75. https://doi.org/10.15585/mmwr.mm6846a5.
17. CDC, Pneumococcal Vaccination. Summary of Who and When to Vaccinate. Centers for Disease Control and Prevention. CDC; 2024. Accessed 2025 April 30. https://www.cdc.gov/vaccines/vpd/pneumo/hcp/who-when-to-vaccinate.html
18. Kobayashi M, Leidner AJ, Gierke R et al. Use of 21-Valent Pneumococcal Conjugate Vaccine Among U.S. Adults: Recommendations of the Advisory

Committee on Immunization Practices - United States, 2024. MMWR Morb Mortal Wkly Rep. 2024;73:793–98. https://doi.org/10.15585/mmwr.mm7336a3.
19. Bonnave C, Mertens D, Peetermans W, Cobbaert K, Ghesquiere B, Deschodt M, et al. Adult vaccination for pneumococcal disease: a comparison of the National guidelines in Europe. Eur J Clin Microbiol Infect Dis. 2019;38(4):785–91. https://doi.org/10.1007/s10096-019-03485-3.
20. European Centre for Disease Prevention and Control. (2024). Vaccine Scheduler: Pneumococcal Disease. Retrieved November 25, 2024, from https://www.ecdc.europa.eu/en/publications-data/ecdc-vaccine-scheduler
21. Generalitat de Catalunya. Calendari de vacunacions sistematiques 2016. Barcelona (SP): Generalitat de Catalunya. Departament de Salut; 2017 [accessed 2025 April 11]. https://canalsalut.gencat.cat/ca/salut-a-z/v/vacunacions/calendari/
22. Vila-Córcoles A, Ochoa-Gondar O, de Diego-Cabanes C, Satué-Gracia EM, Torras-Vives V, Forcadell-Peris MJ, et al. Evaluating clinical effectiveness and impact of anti-pneumococcal vaccination in adults after universal childhood PCV13 implementation in Catalonia, 2017–2018. Vaccine X. 2023;13:100264. https://doi.org/10.1016/j.jvacx.2023.100264.
23. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. World Medical Association. 2018 Jul 09 [accessed 2025 April 03]. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
24. García-Gil Mdel M, Hermosilla E, Prieto-Alhambra D, Fina F, Rosell M, Ramos R, et al. Construction and validation of a scoring system for the selection of high-quality data in a Spanish population primary care database (SIDIAP). Inf Prim Care. 2011;19(3):135–45. https://doi.org/10.14236/jhi.v19i3.806.
25. Ministerio de Sanidad. Conjunto Mínimo Básico de Datos de Hospitalización (CMBD-H). Madrid: Ministerio de Sanidad. Portal estadístico. Área de inteligencia de gestión [accessed 2025 April 11]. https://pestadistico.inteligenciadegestion.sanidad.gob.es/publicoSNS/N/rae-cmbd/cmbd-h
26. Vila-Corcoles A, Ochoa-Gondar O, de Diego C, Satue E, Aragón M, Vila-Rovira A, et al. Evaluating clinical effectiveness of 13-valent Pneumococcal conjugate vaccination against pneumonia among middle-aged and older adults in Catalonia: results from the EPIVAC cohort study. BMC Infect Dis. 2018;18(1):196. https://doi.org/10.1186/s12879-018-3096-7.
27. Torres A, Barberán J, Falguera M, Menéndez R, Molina J, Olaechea P et al. Multidisciplinary guidelines for the management of community-acquired pneumonia [in Spanish]. Med Clin (Barc). 2013;140(5):223.e1-223.e19. Spanish. https://doi.org/10.1016/j.medcli.2012.09.034
28. Hosmer DW, Lemeshow S. Applied survival analysis. Regression modeling of time to event data. New York: Wiley; 1999.
29. Bosco JLF, Silliman RA, Thwin SS, Geiger AM, Buist DSM, Prout MN, et al. A most stubborn bias: no adjustment method fully resolves confounding by indication in observational studies. J Clin Epidemiol. 2010;63:64–74.
30. Farrar JL, Childs L, Ouattara M, Akhter F, Britton A, Pilishvili T, et al. Systematic review and meta- analysis of the efficacy and effectiveness of Pneumococcal vaccines in adults. Pathogens. 2023;12(5):732. https://doi.org/10.3390/pathogens12050732.
31. Kobayashi M, Spiller MW, Wu X, Wang R, Chillarige Y, Wernecke M, et al. Association of pneumococcal conjugate vaccine use with hospitalized pneumonia in medicare beneficiaries 65 years or older with and without medical conditions, 2014 to 2017. JAMA Intern Med. 2023;183(1):40–7. https://doi.org/10.1001/jamainternmed.2022.5472.
32. Kobayashi M, Leidner AJ, Gierke R, Xing W, Accorsi E, Moro P, et al. Recommendations for use of Pneumococcal conjugate vaccines among adults aged ≥ 50 years: recommendations of the advisory committee on immunization Practices - United states, 2024. MMWR Morb Mortal Wkly Rep. 2025;74(1):1–8. https://doi.org/10.15585/mmwr.mm7401a1.
33. Torras-Vives V, de Diego-Cabanes C, Satué-Gracia EM, Forcadell-Peris MJ, Ochoa-Gondar O, Vila-Córcoles Á. Incidence of Pneumococcal and all-cause pneumonia in adults in Catalonia following the implementation of universal Pneumococcal vaccination in children: 2015–2016 vs. 2017–2018. Enferm infecc microbiol clin (Engl Ed). Published Online March. 2025;28. https://doi.org/10.1016/j.eimce.2025.03.005.
34. Ardanuy C, Broner S, Cabezas C, Ciruela P, Izquierdo C, Martínez M et al. Epidemiología de la enfermedad neumocócica invasiva en Cataluña: informe 2021–2022; sistema de notificación microbiológica de Cataluña. Barcelona: Agència de Salut Pública de Catalunya; 2023. Available at: https://saludpublica.gencat.cat/web/.content/minisite/aspcat/vigilancia_salud_publica/SNMC/epidemiologia-malalties-snmc/epidemiologia-de-la-malaltia-pneumoccica-invasiva-a-Catalunya.-Informe-2019-2020.pdf [accessed: 2025 March 09].
35. Marimon JM, Ardanuy C. Epidemiology of pneumococcal diseases in Spain after the introduction of pneumococcal conjugate vaccines. Enferm Infecc Microbiol Clin (Engl Ed). 2021;39(3):142–50. https://doi.org/10.1016/j.eimc.2020.02.016.
36. Nakashima K, Fukushima W. Strategies for pneumococcal vaccination in older adults in the coming era. Hum Vaccin Immunother. 2024;20(1):2328963. https://doi.org/10.1080/21645515.2024.2328963.
37. Narciso AR, Dookie R, Nannapaneni P, Normark S, Henriques-Normark B. *Streptococcus pneumoniae* epidemiology, pathogenesis and control. Nat Rev Microbiol. 2025;23(4):256–71. https://doi.org/10.1038/s41579-024-01116-z.
38. Elias C, Nunes MC, Saadatian-Elahi M. Epidemiology of community-acquired pneumonia caused by *Streptococcus pneumoniae* in older adults: a narrative review. Curr Opin Infect Dis. 2024;37(2):144–53.
39. Streeter AJ, Rodgers LR, Masoli J, Lin NX, Blé A, Hamilton W, et al. Real-world effectiveness of Pneumococcal vaccination in older adults: cohort study using the UK clinical practice research datalink. PLoS ONE. 2022;17(10):e0275642. https://doi.org/10.1371/journal.pone.0275642.
40. Generalitat de Catalunya. Population on 1 January. By age group. Catalunya: Statistical Institute of Catalonia. Annual indicators. Demography•Society. Population figures. 2021 [accessed: 2025 April 11] https://www.idescat.cat/indicadors/?id=anuals%26;n=10329%26;col=1⟨=en
41. Dunne EM, Cilloniz C, von Mollendorf C, Lewnard J, Grant LR, Slack MPE, et al. Pneumococcal vaccination in adults: what can we learn from observational studies that evaluated PCV13 and PPV23 effectiveness in the same population?? Arch Bronconeumol. 2023;59(3):157–64. https://doi.org/10.1016/j.arbres.2022.12.015.
42. Guevara RE, Butler JC, Marston BJ, Plouffe JF, File TM Jr, Breiman RF. Accuracy of ICD-9-CM codes in detecting community-acquired pneumococcal pneumonia for incidence and vaccine efficacy studies. Am J Epidemiol. 1999;149(3):282–9. https://doi.org/10.1093/oxfordjournals.aje.a009804.
43. Ciruela P, Broner S, Izquierdo C, Nogueras MM, Hernández S, Muñoz-Almagro C et al. Epidemiología de la enfermedad neumocócica invasiva en Cataluña. Informe 2017–2018. Barcelona: Agencia de Salud Pública de Cataluña. Departamento de Salud; 2020 [accessed 2025 April. 11]. https://scientiasalut.gencat.cat/bitstream/handle/11351/5457/epidemiologia_malaltia_pneumococcica_catalunya_2017_2018_cas.pdf?sequence=5

Publisher's Note