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Indirect effects of paediatric conjugate vaccines on invasive pneumococcal disease in older adults

Pilar Ciruela[a,b,*], Sonia Broner[a], Conchita Izquierdo[a], Roman Pallarés[c,d], Carmen Muñoz-Almagro[b,e,f], Sergi Hernández[a], Imma Grau[c,d], Angela Domínguez[b,g], Mireia Jané[a,b], The Catalan Working Group on Invasive Pneumococcal Disease[1]

[a] Agència de Salut Pública de Catalunya, Generalitat de Catalunya, C/Roc Boronat, 81–95, 08005 Barcelona, Spain
[b] CIBER de Epidemiología y Salud Pública (CIBERESP), Instituto de Salud Carlos III, C/Monforte de Lemos, 3–5, 28029 Madrid, Spain
[c] Hospital Universitari Bellvitge, Universitat de Barcelona, C/Feixa Llarga s/n 08907, L'Hospitalet, Barcelona, Spain
[d] CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, C/Monforte de Lemos, 3–5, 28029 Madrid, Spain
[e] Hospital Universitari Sant Joan de Déu, Pg. Sant Joan de Déu 2, 08950 Esplugues, Barcelona, Spain
[f] Department of Medicine, Universitat Internacional de Catalunya, C/Josep Trueta, s/n 08195 Sant Cugat del Vallès, Barcelona, Spain
[g] Departament de Medicina, Universitat de Barcelona, C/Casanova, 143, 08036 Barcelona, Spain

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ABSTRACT

Objectives: The aim of this study was to assess the indirect effect of paediatric 13-valent pneumococcal conjugate vaccine (PCV13) vaccination on people ≥65 years of age with invasive pneumococcal disease (IPD) in Catalonia and to determine factors predictive of mortality.
Methods: During 2014–2016, 1285 IPD cases were reported to the Public Health Agency of Catalonia. The indirect effect of paediatric PCV13 vaccination was calculated by comparing the incidence rate (IR) in 2016 (PCV13 year) with that in 2009 (pre-PCV13). Predictors of mortality were determined using multivariate logistic regression.
Results: Comparing 2016 and 2009, IPD decreased by 19% (IR 40.1 and 32.5 per 100 000 person-years, respectively). PCV13 serotypes decreased by 57% (IR 23.7 and 10.1), while non-PCV13 serotypes increased by 36% (IR 16.4 and 22.4). During 2014–2016, the mortality rate was 17.5%, and mortality was associated with age ≥85 years (adjusted odds ratio (aOR) 2.91, 95% confidence interval (CI) 1.89, 4.48), meningitis (aOR 2.29, 95% CI 1.25, 4.19), non-focal bacteraemia (aOR 3.73, 95% CI 2.00, 6.94), and ≥1 high-risk condition (aOR 1.89, 95% CI 1.08, 3.32). PPV23non13 serotypes were associated with lower mortality than PCV13 serotypes (aOR 0.54, 95% CI 0.34, 0.86).
Conclusions: The incidence of IPD in people ≥65 years of age decreased after the introduction of paediatric PCV13, and this was due to a reduction in PCV13 serotypes, although an increase in non-PCV13 serotypes was observed. Mortality was associated with age, meningitis, non-focal bacteraemia, ≥1 high-risk condition, and PCV13 serotypes.

* Corresponding author at: Agència de Salut Pública de Catalunya, Generalitat de Catalunya, C/Roc Boronat, 81–95, 08005 Barcelona, Spain.
E-mail addresses: pilar.ciruela@gencat.cat (P. Ciruela), memergents@gencat.cat (S. Broner), controlepidemiologic@gencat.cat (C. Izquierdo), rpallares@ub.edu (R. Pallarés), cma@hsjdbcn.org (C. Muñoz-Almagro), snmc@gencat.cat (S. Hernández), igrau@ub.edu (I. Grau), angela.dominguez@ub.edu (A. Domínguez), mireia.jane@gencat.cat (M. Jané).

[1] The Catalan Working Group on Invasive Pneumococcal Disease: Cristina Esteva, Departament de Microbiologia Molecular, Hospital Universitari Sant Joan de Déu, Pg. Sant Joan de Déu, 2, 08950 Esplugues, Barcelona, Spain. Mariona Fernández de Sevilla, Servei de Pediatria, Hospital Universitari Sant Joan de Déu, Pg. Sant Joan de Déu, 2, 08950 Esplugues, Barcelona, Spain. Desiree Henares, Departament de Microbiologia Molecular, Hospital Universitari Sant Joan de Déu, Pg. Sant Joan de Déu, 2, 08950 Esplugues, Barcelona, Spain. Carmen Ardanuy, Hospital Universitari de Bellvitge, Universitat de Barcelona, C/Feixa Llarga s/n, 08907 L'Hospitalet, Barcelona, Spain. Francesc Marco, Servei de Microbiologia, Hospital Clínic de Barcelona, C/Villarroel, 170, 08036 Barcelona, Spain. Nuria Margall, Servei de Microbiologia, Hospital Santa Creu i Sant Pau, C/de Sant Quintí, 89, 08041 Barcelona, Spain. Araceli González-Cuevas, Laboratori de Microbiologia, Hospital General del Parc Sanitari Sant Joan de Déu, Camí Vell de la Colònia, 25, 08830 Sant Boi de Llobregat, Barcelona, Spain. Alvaro Díaz, Servei de Pediatria i Recerca, Fundació Hospital de Nens de Barcelona, C/Consell de Cent, 437, 08009 Barcelona,

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Introduction

Streptococcus pneumoniae is a leading cause of severe disease worldwide, causing around one million deaths annually that affect mainly children and older people (Liu et al., 2016). Immunization of children with pneumococcal conjugate vaccines (PCV) has reduced the incidence of invasive pneumococcal disease (IPD) due to PCV serotypes in children, as well as in unvaccinated age groups, due to herd protection. However, other non-vaccine serotypes have emerged in children and adults (Whitney et al., 2003; Pilishvili et al., 2010; Pelton et al., 2004).

The 23-valent pneumococcal polysaccharide vaccine (PPV23) has been indicated for people aged ≥65 years and those aged <65 years at increased risk of IPD (Pebody et al., 2005) since 1983. In 2012, the Advisory Committee on Immunization Practices recommended one dose of PCV13 vaccine followed by one dose of PPV23 at least 8 weeks later in people aged ≥19 years with high-risk conditions (Centers for Disease Control and Prevention (CDC), 2012).

In Catalonia, Spain, PPV23 was introduced for persons aged >2 years with a high-risk condition and older adults in 1999 (Generalitat de Catalunya, 2014). The 13-valent pneumococcal conjugate vaccine (PCV13) was included in the routine vaccination schedule for children in 2016 and recommended for persons with high-risk conditions. Prior to this date, children aged <5 years with risk factors were vaccinated with PCV13 free of charge, and in addition, other children were vaccinated with available PCVs according to the recommendation of their paediatrician (Generalitat de Catalunya, Departament de Salut, 2018).

Factors related to the host, such as age and underlying diseases (Hausdorff et al., 2000; Feikin et al., 2000; Niederman et al., 2001; Moroney et al., 2001; Yu et al., 2003), and factors related to the bacteria (serotype) (Gilbert and Fine 1994; Henriques et al., 2000) have been associated with an increased susceptibility to IPD and greater mortality in adults.

The objectives of this study were to assess the indirect effect of PCV13 vaccination in children on people ≥65 years of age in Catalonia and to determine the factors predictive of the IPD case fatality rate in this age group.

Methods

Study population

The Catalan population ≥65 years of age was 1,217,519 in 2009 and increased to 1,379,277 by 2016 (Institut d'Estadística de Catalunya, 2019).

Case definition

An IPD case was defined as a patient aged ≥65 years with clinical symptoms of infection (e.g., pneumonia, meningitis) together with *S. pneumoniae* isolation by culture or *S. pneumoniae* DNA detection by PCR or antigen detection in a normally sterile site (e.g., blood, cerebrospinal fluid, pleural fluid, joint fluid, peritoneal fluid, or lung tissue). Only one IPD episode per patient was included, unless clinical sample collection dates were separated by >30 days or the serotypes identified differed.

Vaccination policy and vaccine uptake

The estimated 7-valent PCV (PCV7) coverage in Catalonia was 58.7% in children aged <5 years (2007–2009) (Ciruela et al., 2013a). PCV13 and 10-valent PCV coverage in children aged <2 years was 64% and 4%, respectively (2012–2013) (Savulescu et al., 2017). Estimated PPV23 coverage was around 50% in older people in 2005–2007 (Dominguez et al., 2010).

Spain. Maria Teresa Martin, Servei de Microbiologia, Hospital Universitari Vall d'Hebron, Pg. De la Vall d'Hebron, 119–129, 08035 Barcelona, Spain. Jaume Llaberia, Laboratori de Microbiologia, SCIAS Hospital de Barcelona, C/Diagonal, 660, 08034 Barcelona, Spain. Margarida Curriu, Servei de Microbiologia, Hospital Sant Bernabé, Ctra. de Ribes, s/n, 08600 Berga, Spain. Carme Gallés, Unitat de Microbiologia, Servei d'Anàlisis Clíniques, Corporació de Salut del Maresme i la Selva, C/Sant Jaume, 209–217, 08370 Calella, Barcelona, Spain. Elisenda Capdevila, Unitat de Microbiologia, Servei d'Anàlisis Clíniques, Corporació de Salut del Maresme i la Selva, C/Sant Jaume, 209–217, 08370 Calella, Barcelona, Spain. Paula Gassiot, Àrea de Microbiologia, Laboratori d'Anàlisis Clíniques, Hospital de Figueres, Rda. Rector Arolas, s/n, 17600 Figueres, Girona, Spain. Matilde Martínez-Zurita, Àrea de Microbiologia, Laboratori Clínic - Institut Català de la Salut Girona, Hospital Universitari Dr. Josep Trueta, Av. França, s/n, 17007 Girona, Spain. Carmina Martí, Laboratori de Microbiologia, Hospital General de Granollers, Av. Francesc Ribas, s/n, 08402 Granollers, Barcelona, Spain. Montserrat Morta, Servei de Microbiologia, Hospital Sant Joan de Déu, Fundació ALTHAIA, C/Dr. Joan Soler, s/n, 08243 Manresa, Barcelona, Spain. Goretti Sauca, Servei d'Análisis Clíniques, Secció de Microbiologia, Hospital de Mataró, Ctra. de Cirera, 230, 08304 Mataró, Barcelona, Spain. Asunción Gassós, Servei de Microbiologia, Sant Joan de Déu de Martorell, Av. Mancomunitats Comarcals, 1–3, 08760 Martorell, Barcelona, Spain. Esther Sanfeliu, Servei d'Anàlisis Clíniques, Secció de Microbiologia, Hospital d'Olot Comarcal de la Garrotxa, Av. dels Països Catalans, 86, 17800 Olot, Girona, Spain. Frederic Ballester, Laboratori de Referencia Sud, Hospital Sant Joan de Reus, Av. Dr Josep Laporte, 2, 43204 Reus, Tarragona, Spain. Isabel Pujol, Laboratori de Referencia Sud, Hospital Sant Joan de Reus, Av. Dr Josep Laporte, 2, 43204 Reus, Tarragona, Spain. Montserrat Olsina, Laboratori d'Anàlisis Clínics, Microbiologia, Hospital General de Catalunya, C/Pedro i Pons, 1, 08190 Sant Cugat del Vallès, Barcelona, Spain. Xavier Raga, Laboratori de Microbiologia, Hospital Sant Pau i Santa Tecla, Rambla Vella, 14, 43003 Tarragona, Spain. Frederic Gómez-Bertomeu, Àrea de Microbiologia, Laboratori Clínic ICS - Camp de Tarragona, Hospital Joan XXIII, C/Dr. Mallafrè Guasch, 4, 43005 Tarragona, Spain. Mar Olga Pérez-Moreno, Àrea de Microbiologia, Laboratori Clínic ICS - Terres de l'Ebre, Hospital Verge de la Cinta, C/de les Esplanetes, 14, 43500 Tortosa, Tarragona, Spain. Anna Vilamala, Servei de Microbiologia, Consorci Hospitalari de Vic, C/Francesc Pla 'El Vigatà', 1, 08500 Vic, Barcelona, Spain. Maria Navarro, Servei de Microbiologia, Consorci Hospitalari de Vic, C/Francesc Pla 'El Vigatà', 1, 08500 Vic, Barcelona, Spain. Mercè Ribelles, Secció Microbiologia, Servei d'Anàlisis Clíniques, Hospital Universitari Arnau de Vilanova de Lleida, Av. Rovira Roure, 80, 25198 Lleida, Barcelona, Spain. Mercè Garcia, Secció Microbiologia, Servei d'Anàlisis Clíniques, Hospital Universitari Arnau de Vilanova de Lleida, Av. Rovira Roure, 80, 25198 Lleida, Barcelona, Spain. Eduardo Padilla, Laboratori de Referència Catalunya, C/de la Selva, 10, 08820 Prat de Llobregat (El), Barcelona, Spain. Nuria Prim, Laboratori de Referència Catalunya, C/de la Selva, 10, 08820 Prat de Llobregat (El), Barcelona, Spain. Dionisia Fontanals, Secció de Microbiologia, Parc Taulí Hospital Universitari, Institut d'Investigació i Innovació Parc Taulí I3PT, UAB, C/Parc del Taulí, 1, 08208 Sabadell, Barcelona, Spain. Isabel Sanfeliu, Secció de Microbiologia, Parc Taulí Hospital Universitari, Institut d'Investigació i Innovació Parc Taulí I3PT, UAB C/ Parc del Taulí, 1, 08208 Sabadell, Barcelona, Spain. Miguel Angel Benítez, Servei de Microbiologia, CLILAB Diagnòstics, C/Espirall, s/n, 08720 Vilafranca del Penedès, Barcelona, Spain. Eulalia Jou, Servei de Microbiologia, CLILAB Diagnòstics, C/Espirall, s/n, 08720 Vilafranca del Penedès, Barcelona, Spain. Carmina Sanjosé, Servei de Microbiologia, CLILAB Diagnòstics, C/Espirall, s/n 08720 Vilafranca del Penedès, Barcelona, Spain. Montserrat Giménez, Laboratori Clínic Metropolitana Nord, Hospital Universitari Germans Trias i Pujol, Ctra. de Canyet, s/n 08916 Badalona, Barcelona, Spain. Maria Dolores Quesada, Laboratori Clínic Metropolitana Nord, Hospital Universitari Germans Trias i Pujol, Ctra. de Canyet, s/n 08916 Badalona, Barcelona, Spain. Jose Carlos de la Fuente, Servei de Microbiologia, Hospital Comarcal Móra d'Ebre, C/de Benet Messeguer, s/n 43770 Móra d'Ebre, Tarragona, Spain. Ana Calderon, Servei de Microbiologia, Hospital Municipal de Badalona, C/Via Augusta, 9–13, 08911 Badalona, Barcelona, Spain. Percy Juan Ayala, Servei de Microbiologia, Clínica Terres de l'Ebre, Pl. De Joaquim Bau, 6–8, 43500 Tortosa, Tarragona, Spain. Josefa Pérez-Jové, Departament de Microbiologia, Catlab - Centre Analítiques Terrassa, AIE, Parc Logístic de Salut, Vial Sant Jordi, s/n, 08232 Viladecavalls, Barcelona, Spain. Ana Blanco, Departament de Microbiologia, Catlab - Centre Analítiques Terrassa, AIE, Parc Logístic de Salut, Vial Sant Jordi, s/n 08232, Viladecavalls, Barcelona, Spain. Conchita Balado, Departament de Microbiologia Clínica, Laboratori d'Anàlisis Dr. F Echevarne, C/de los Castillejos, 365, 08025 Barcelona, Spain. Ines Valle, Departament de Microbiologia Clínica, Laboratori d'Anàlisis Dr. F Echevarne, C/de los Castillejos, 365, 08025 Barcelona, Spain. Maria Teresa Bastida, Laboratori de Microbiologia, Fundació Hospital Esperit Sant, C/Pons i Rabadà s/n, 08923 Santa Coloma de Gramenet, Spain. Olga Gonzalez-Moreno, Laboratori de Microbiologia, SYNLAB Diagnósticos Globales S.A.U., C/Verge de Guadalupe, 18, 08950 Esplugues de Llobregat, Spain. Amaia Oteiza Ubanell, Laboratori d'Anàlisis Clíniques, Hospital de Palamós, C/Hospital, 36, 17230 Palamós, Spain.

Surveillance system

An active and retrospective study of all laboratory-confirmed IPD cases reported to the Microbiological Reporting System (MRS) of the Public Health Agency of Catalonia was conducted. The MRS involves 50 centres, representing over 85% of hospital beds in public hospitals. All Catalonian reference hospitals were included. In addition, cases from some private hospitals that send strains to regional and national reference laboratories were also recovered in order to study the serotypes (Ciruela et al., 2018).

The variables included were age, sex, clinical form, serotype and antibiotic susceptibility. Clinical form was stratified into pneumonia, empyema, non-focal bacteraemia, meningitis, and other clinical forms. Serotyping and antibiotic susceptibility testing were performed by the Public Health Support Laboratory of Catalonia (Sant Joan de Déu University Hospital) and the National Centre for Microbiology – Instituto de Salud Carlos III (Madrid, Spain) as described previously (Fenoll et al., 1997). Meningeal breakpoints for penicillin were considered for the epidemiological analysis (The European Committee on Antimicrobial Susceptibility Testing, 2015). Isolates with intermediate or high-level resistance were defined as non-susceptible.

The date of hospitalization, intensive care unit (ICU) admission, IPD-predisposing comorbidities, vaccination history (PPV23, influenza vaccine in the current season), and mortality (30-day mortality) were collected from the medical records. Comorbidities were divided into two mutually-exclusive categories: (1) high risk, including chronic renal failure, HIV, immunodeficiency (medically induced or innate), asplenia, haematological or metastatic malignancies, CSF leak, and prior neurosurgery, and (2) at risk, including diabetes mellitus, congestive heart failure, chronic lung disease, cirrhosis, smoking, and alcoholism (Centers for Disease Control and Prevention (CDC), 2012). The presence of ≥2 comorbidities was classified as '>1 high-risk condition', if one of them was a high-risk condition, and as '>1 at-risk condition' otherwise.

The length of hospital stay was classified as <15 days or ≥15 days. The time since the last PPV23 dose was classified as <5 years or ≥5 years. Cases were considered vaccinated with PPV23 or influenza vaccine when they had received a dose of either vaccine at least 14 days before symptom onset.

Data analysis

The data analysis was performed by comparison of the year 2009 data (baseline year prior to marketing of PCV13) to the year 2016 data, when PCV13 was included in the paediatric vaccination schedule. Some data from 2014, 2015, and 2016 were also included when performing the analysis of pneumococcal serotypes, in order to increase the sample size. The variables studied were the number of cases, incidence rates (IR), sex, age group, clinical form, serotype categories, and antibiotic susceptibility. The age groups considered were 65–74 years, 75–84 years, and ≥85 years. Serotypes were grouped into four categories by vaccine coverage: PCV7 (included serotypes: 4, 6B, 9V, 14, 18C, 19F, and 23F), PCV13non7 (included serotypes: 1, 3, 5, 6A, 7F, and 19A), PPV23non13 (included serotypes: 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F), and nonPPV23 serotypes (serotypes not included in PPV23 and not serotype 6A).

The indirect effect of PCV13 in people ≥65 years of age was calculated by comparing the IR in 2016 with the IR in 2009 by serotype category and age group. For cases with missing serotype information, it was assumed that the serotype distribution was the same as among cases with the known serotype in the same year and age group. Changes in the estimated IR were assessed by incidence rate ratios (IRR) with 95% confidence intervals (CI) and were expressed as the percentage change in incidence. Proportions were compared using the Chi-square test or Fisher's exact test, as appropriate.

To determine predictors of the case fatality rate during 2014–2016, multivariate logistic regression was used. The model included all variables with a value of $p < 0.2$ in the univariate regression analyses. The odds ratios (OR) and 95% CI were calculated.

Two-sided p-values of <0.05 were considered statistically significant. The analyses were conducted using the IBM SPSS Statistics version 19.0 (IBM Corp., Armonk, NY, USA) and R 2.13.0 (R Development Core Team 2014).

Table 1
Changes in demographic, clinical, and microbiological characteristics of patients ≥65 years of age with IPD before and after the introduction of PCV13; Catalonia, 2009 and 2016.

	2009 (n = 488) n (%)	2016 (n = 448) n (%)	p-Value
Age group (years)			
65–74	168 (34.4)	168 (37.5)	0.340
75–84	202 (41.4)	144 (32.1)	0.004
≥85	118 (24.2)	136 (30.4)	0.039
Sex			
Male	264 (54.1)	252 (56.3)	0.512
Clinical presentation			
All pneumonia	409 (83.8)	369 (82.4)	0.600
Empyema	30 (6.1)	18 (4.0)	0.181
Non-focal bacteraemia	37 (7.6)	28 (6.3)	0.443
Meningitis	26 (5.3)	38 (8.5)	0.069
Other forms[a]	16 (3.3)	13 (2.9)	0.851
Hospitalization ($^{*}n$ = 357; $^{**}n$ = 428)			
Yes	350 (98.0)	416 (97.2)	0.492
Length of hospital stay ($^{*}n$ = 331; $^{**}n$ = 410)			
≥15 days	85 (25.6)	287 (24.4)	0.189
ICU admission ($^{*}n$ = 225; $^{**}n$ = 414)			
Yes	84 (25.4)	87 (21.2)	1
Underlying diseases ($^{*}n$ = 302; $^{**}n$ = 414)			
At risk	157 (52)	213 (49.6)	0.548
Chronic cardiovascular disease	58 (19.2)	57 (13.3)	0.039
Chronic lung disease	12 (4.0)	18 (4.2)	1
Diabetes	19 (6.3)	34 (7.9)	0.470
Cirrhosis	4 (1.3)	5 (1.2)	1
Alcoholism	1 (0.3)	1 (0.2)	1
Smoking	3 (1.0)	1 (0.2)	0.388
CSF leakage	0 (0.0)	2 (0.5)	0.639
>1 at-risk condition	60 (19.9)	95 (22.1)	0.520
High risk	102 (33.8)	159 (37)	0.389
Chronic renal disease	4 (1.3)	19 (4.4)	0.018
Immunodeficiency	34 (11.3)	25 (5.8)	0.009
Asplenia	0 (0.0)	0 (0.0)	1
Transplant	1 (0.3)	0 (0.0)	0.860
>1 high-risk condition	63 (20.9)	115 (26.8)	0.067
No condition	43 (14.2)	57 (13.3)	0.744
Influenza vaccination ($^{*}n$ = 445; $^{**}n$ = 439)			
Yes	199 (44.7)	202 (46.0)	0.736
PPV23 vaccination			
Vaccinated ($^{*}n$ = 445; $^{**}n$ = 439)	184 (41.3)	270 (61.5)	<0.001
PPV23 ≥ 5 years	112 (60.9)	216 (80.0)	<0.001
PPV23 < 5 years	72 (39.1)	54 (20.0)	<0.001
Non-vaccinated	261 (58.7)	169 (38.5)	<0.001
Penicillin ($^{*}n$ = 420; $^{**}n$ = 372)			
Non-susceptible	104 (24.8)	97 (26.1)	0.683
Cefotaxime ($^{*}n$ = 420; $^{**}n$ = 372)			
Non-susceptible	47 (11.2)	51 (13.7)	0.334

Abbreviations: IPD, invasive pneumococcal disease; PCV13, 13-valent pneumococcal conjugate vaccine; CSF leakage, cerebral spinal fluid leakage; ICU, intensive care unit; PPV23, 23-valent pneumococcal polysaccharide vaccine.

[a] Other forms: abdominal (15 cases), osteoarticular (10 cases), cellulitis (3 cases), endocarditis (1 case).

* 2009.

** 2016.

Results

Characteristics of IPD in people older than 64 years of age

A total of 488 IPD cases were reported in 2009 compared to 448 cases in 2016 (Table 1). The highest number of cases was in the 75–84 years age group in 2009 (41.4%) and in the 65–74 years age group in 2016 (37.5%). There was an increase in cases in the ≥85 years age group (24.2% vs. 30.4%; $p = 0.039$) and a decrease in the 75–84 years age group (41.4% vs. 32.1%; $p = 0.004$) in 2016 compared to 2009. The predominant clinical form was pneumonia (83.8% in 2009, 82.4% in 2016). More than a quarter of patients were admitted to the ICU in 2009 (25.4%) and 21.2% in 2016. There was no change between 2009 and 2016 regarding clinical forms, hospitalization, and ICU admission.

One hundred and fifty-seven cases (52.0%) had ≥1 at-riskcomorbidity in 2009 compared to 213 cases (49.6%) in 2016. Furthermore, 102 (33.8%) cases in 2009 compared to 159 (37.0%) cases in 2016 had ≥1 high-risk comorbidity. There were no significant differences between these categories in the years analysed. Only chronic cardiovascular disease (19.2% vs. 13.3%; $p = 0.039$) and immunodeficiency (11.3% vs. 5.8%; $p = 0.009$) declined in 2016, whereas chronic renal disease increased (1.3% vs. 4.4%; $p = 0.018$). IPD cases vaccinated with PPV23 increased in 2016 (41.3% vs. 61.5%; $p < 0.001$), although cases vaccinated within the previous 5 years declined (39.1% vs. 20.0%; $p < 0.001$).

Antibiotic susceptibility testing was performed on 420 (86.1%) isolates in 2009 and 372 (83.0%) isolates in 2016; of these, 24.8% and 26.1% ($p = 0.683$), respectively, were non-susceptible to penicillin and 11.2% and 13.7% ($p = 0.334$), respectively, were non-susceptible to cefotaxime.

Indirect effect of PCV13 on IPD in people older than 64 years of age

During 2014–2016, the IPD IR was between 29.0 and 33.0 per 100 000 person-years in 2014 and 2015, respectively (Figure 1). The highest incidence was in the age group ≥85 years (52.0 in 2014 and 63.2 in 2016). The serotype was available in 1114 (86.7%) cases. The estimated serotypes included in PCV13, PPV23non13, and non-vaccine serotypes represented 34.8%, 35.0%, and 30.2% of cases, respectively. The most frequent serotypes were 3 (11.6%), 8 (8.3%), 14 (7.3%), 12F (6.8%), 22F (5.2%), and 19A (4.9%), which are included in PCV13 and PPV23 (Figure 2A, B).

Changes in estimated IR and serotype groups between 2009 and 2016 are shown in Table 2. Global IPD IR decreased by 19% in 2016 (40.1 and 32.5 per 100 000 person-years, respectively; IRR 0.81, 95% CI 0.71, 0.92). The incidence of serotypes included in PCV13 showed a decrease of 57% in 2016, mainly due to the PCV13non7 serotypes (70%). However, non-PCV13 serotypes increased by 36%, especially due to PPV23non13 serotypes (80%).

PCV13 serotypes decreased in all age groups, between 51% in people aged ≥85 years and 60% in those aged 75–84 years. Non-PCV13 serotypes increased in all age groups, but the difference was statistically significant only in the 65–74 years age group, increasing by 62% (10.8 and 17.5 per 100 000 person-years in 2009 and 2016, respectively; IRR 1.62, 95% CI 1.19, 2.23).

Predictors of the case fatality rate

During 2014–2016, there were 219/1253 fatal cases (17.5%), which increased with age from 12.2% in people aged 65–74 years to 25.7% in those aged ≥85 years (Table 3). The case fatality rate was higher in people with comorbidities (at-risk 15.6% and high-risk 21.2%) than in healthy people (13.9%). In the univariate analysis, older age,

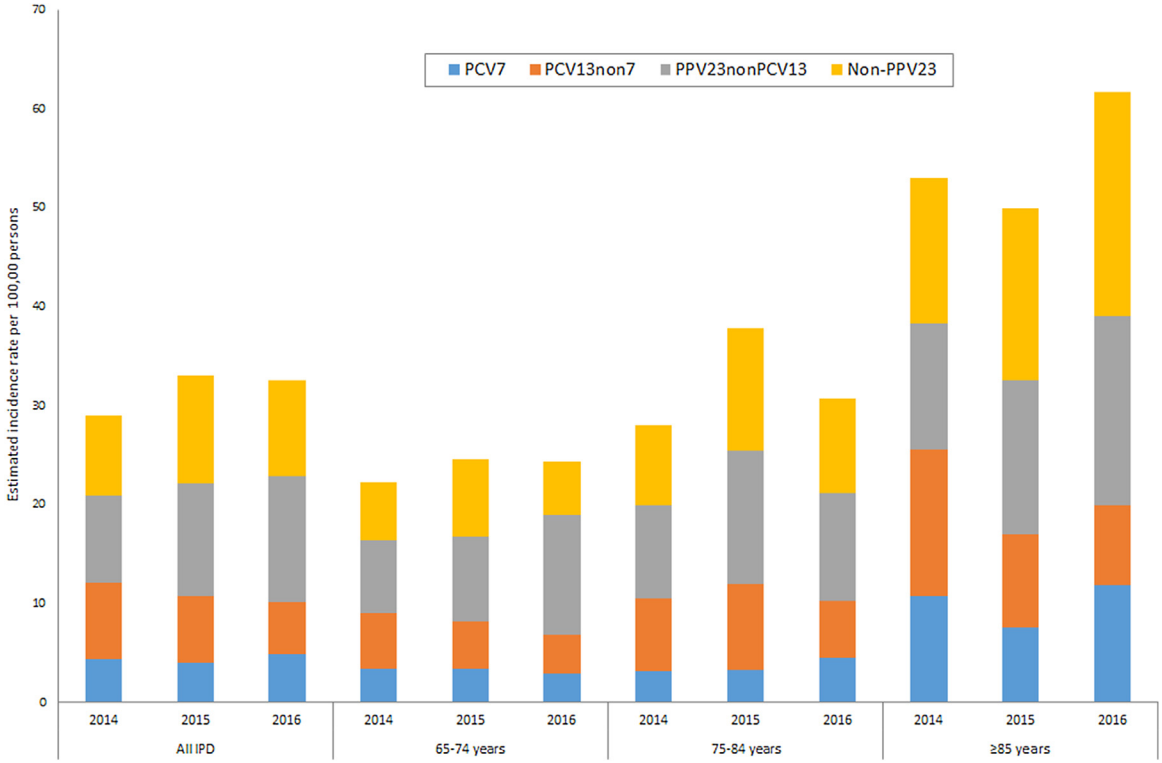


Figure 1. Estimated IPD incidence rate by year, age group and vaccine serotypes in patients aged ≥65 years. Catalonia, 2014–2016.
Abbreviations: IPD, invasive pneumococcal disease; PCV7 serotypes, serotypes included in 7-valent pneumococcal conjugate vaccine; PCV13non7 serotypes, additional serotypes included in 13-valent pneumococcal conjugate vaccine; PPV23non13, additional serotypes included in 23-valent pneumococcal conjugate vaccine; Non-PPV23, serotypes not included in 23-valent pneumococcal polysaccharide vaccine and not 6A.

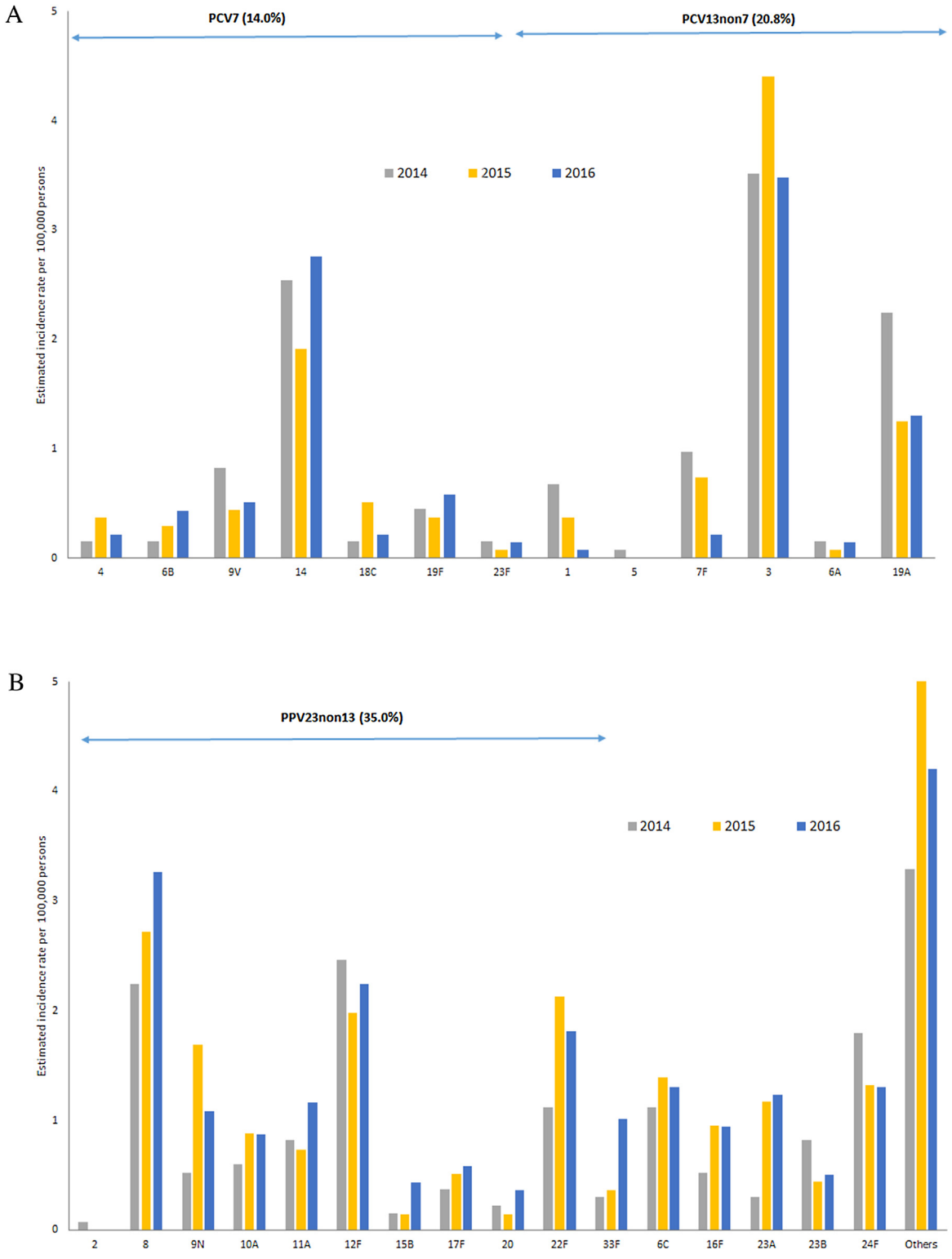


Figure 2. (A) Estimated IPD incidence rate caused by PCV13 serotypes in patients aged ≥65 years. Catalonia, 2014–2016. (B) Estimated IPD incidence rate caused by PPV23non-PCV13 serotypes and non-PPV23 serotypes in patients aged ≥65 years. Catalonia, 2014–2016.
Abbreviations: IPD, invasive pneumococcal disease; PCV7 serotypes, serotypes included in 7-valent pneumococcal conjugate vaccine; PCV13non7 serotypes, additional serotypes included in 13-valent pneumococcal conjugate vaccine; PPV23non13, additional serotypes included in 23-valent pneumococcal conjugate vaccine.

high-risk conditions, and clinical forms such as meningitis, non-focal bacteraemia, and other clinical forms were associated with greater mortality. IPD due to PPV23non13 serotypes had a lower case fatality rate than PCV13 serotypes, whereas non-susceptibility to penicillin and cefotaxime were risk factors for mortality.

Age, clinical form, high-risk condition, serotype by vaccine type, and antibiotic susceptibility to penicillin and cefotaxime had a p-value of <0.2 in the univariate analysis and were included in the final regression model. The case fatality rate showed a significant difference in people aged ≥85 years compared to those aged 65–74

Table 2
Changes in estimated incidence rate of IPD by vaccine serotypes in patients ≥65 years of age before and after the introduction of PCV13 and estimates of the indirect effect; Catalonia, 2009 and 2016.

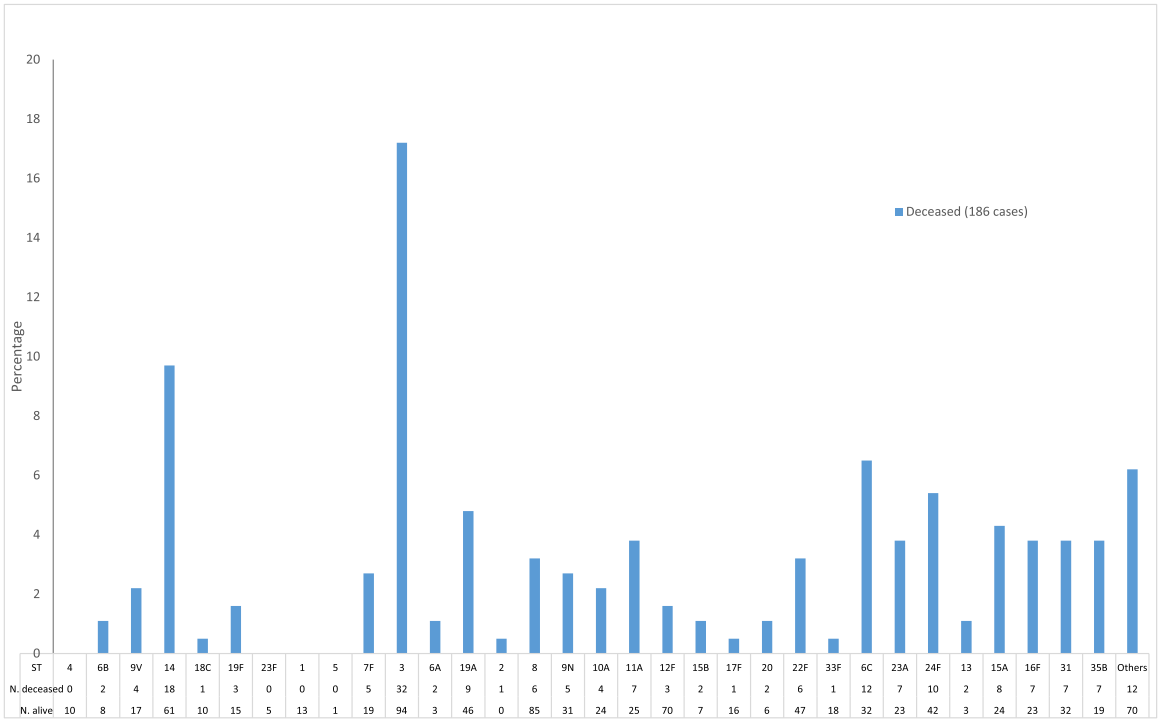
Age and serotype categories	2009		2016		IRR (95% CI)	Indirect effect estimates[a] % (95% CI)
	Estimated (raw) cases	IR	Estimated (raw) cases	IR		
≥65 years	488	40.1	448	32.5	0.81 (0.71, 0.92)	19 (8, 29)
PCV13	288 (246)	23.7	139 (116)	10.1	0.43 (0.35, 0.52)	57 (48, 65)
PCV7	79 (70)	6.5	67 (56)	4.9	0.75 (0.53, 1.05)	25 (−5, 47)
PCV13non7	209 (176)	17.2	72 (60)	5.2	0.30 (0.23, 0.40)	70 (60, 77)
Non-PCV13	200 (178)	16.4	309 (257)	22.4	1.36 (1.14, 1.64)	−36 (−64, −14)
PPV23non13	87 (78)	7.1	177 (145)	12.8	1.8 (1.38, 2.35)	−80 (−135, −38)
Non-PPV23	113 (100)	9.3	132 (112)	9.6	1.03 (0.80, 1.34)	−3 (−34, 20)
65–74 years	168	28.4	168	24.3	0.86 (0.69, 1.07)	14 (−7, 31)
PCV13	104 (92)	17.6	47 (39)	6.8	0.39 (0.27, 0.55)	61 (45, 73)
PCV7	33 (29)	5.6	20 (16)	2.9	0.52 (0.28, 0.93)	48 (7, 72)
PCV13non7	71 (63)	12.0	27 (23)	3.9	0.33 (0.20, 0.51)	67 (49, 80)
Non-PCV13	64 (57)	10.8	121 (104)	17.5	1.62 (1.19, 2.23)	−62 (−123, −19)
PPV23non13	29 (25)	4.9	84 (71)	12.2	2.48 (1.61, 3.92)	−148 (−292, −61)
Non-PPV23	35 (32)	5.9	37 (33)	5.4	0.91 (0.55, 1.48)	9 (−48, 45)
75–84 years	202	43.4	144	30.7	0.71 (0.57, 0.88)	29 (12, 43)
PCV13	118 (97)	25.4	48 (39)	10.2	0.4 (0.28, 0.57)	60 (43, 72)
PCV7	26 (23)	5.6	21 (17)	4.5	0.80 (0.43, 1.48)	20 (−42, 55)
PCV13non7	92 (74)	19.8	27 (22)	5.8	0.29 (0.18, 0.45)	71 (55, 81)
Non-PCV13	84 (72)	18.1	96 (73)	20.5	1.13 (0.84, 1.54)	−13 (−54, 16)
PPV23non13	38 (33)	8.2	51 (38)	10.9	1.33 (0.86, 2.08)	−33 (−108, 14)
Non-PPV23	46 (39)	9.9	45 (35)	9.6	0.97 (0.63, 1.50)	3 (−50, 37)
≥85 years	118	73	136	61.6	0.84 (0.65, 1.09)	16 (−9, 35)
PCV13	66 (57)	40.8	44 (38)	19.9	0.49 (0.33, 0.73)	51 (27, 67)
PCV7	20 (18)	12.4	26 (23)	11.8	0.95 (0.51, 1.80)	5 (−80, 49)
PCV13non7	46 (39)	28.5	18 (15)	8.2	0.29 (0.16, 0.50)	71 (50, 84)
Non-PCV13	52 (49)	32.2	92 (80)	41.7	1.30 (0.91, 1.86)	−30 (−86, 9)
PPV23non13	20 (20)	12.4	42 (36)	19.0	1.54 (0.88, 2.77)	−54 (−177, 12)
Non-PPV23	32 (29)	19.8	50 (44)	22.7	1.14 (0.72, 1.84)	−14 (−84, 28)

Abbreviations: IPD, invasive pneumococcal disease; IR, incidence rate; IRR, incidence rate ratio; CI, confidence interval; PCV13, serotypes included in the 13-valent pneumococcal conjugate vaccine; PCV7, serotypes included in the 7-valent pneumococcal conjugate vaccine; PCV13non7, additional serotypes included in the 13-valent pneumococcal conjugate vaccine; Non-PCV13, serotypes not included in the 13-valent pneumococcal conjugate vaccine; PPV23non13, additional serotypes included in the 23-valent pneumococcal conjugate vaccine; Non-PPV23, serotypes not included in the 23-valent pneumococcal polysaccharide vaccine and not 6A.
[a] Note: A negative indirect effect indicates an increased incidence, while a positive effect indicates a decrease effect.

Table 3
Predictors of death in IPD patients ≥65 years of age; Catalonia, 2014–2016.

		Death		OR (95% CI)	*p*-Value	aOR* (95% CI)	*p*-Value
		Yes (*n* = 219) *n* (%)	No (*n* = 1034) *n* (%)				
Age group (years)	65–74 (*n* = 467)	57 (12.2)	410 (87.8)	1		1	
	75–84 (*n* = 440)	73 (16.6)	367 (83.4)	1.43 (0.98, 2.08)	0.060	1.50 (0.97, 2.32)	0.068
	≥85 (*n* = 346)	89 (25.7)	257 (74.3)	2.49 (1.73, 3.60)	<0.001	2.91 (1.89, 4.48)	<0.001
Sex	Female (*n* = 556)	103 (18.5)	453 (81.5)	1			
	Male (*n* = 697)	116 (16.6)	581 (83.4)	1.14 (0.85, 1.53)	0.384		
Clinical presentation	All pneumonia (*n* = 1031)	156 (15.1)	875 (84.9)	1		1	
	Meningitis (*n* = 99)	24 (24.2)	75 (75.8)	1.80 (1.10, 2.93)	0.019	2.29 (1.25, 4.19)	0.007
	Non-focal bacteraemia (*n* = 68)	24 (35.3)	44 (64.7)	3.06 (1.81, 5.18)	<0.001	3.73 (2.00, 6.94)	<0.001
	Other forms (*n* = 55)	15 (27.3)	40 (72.7)	2.00 (1.13, 3.90)	0.018	1.60 (0.76, 3.41)	0.219
Comorbidities	No risk condition (*n* = 180)	25 (13.9)	155 (86.1)	1		1	
	>1 at-risk condition (*n* = 584)	91 (15.6)	493 (84.4)	1.14 (0.71, 1.85)	0.580	1.21 (0.69, 2.10)	0.508
	>1 high-risk condition (*n* = 468)	99 (21.2)	369 (78.8)	1.66 (1.03, 2.68)	0.037	1.89 (1.08, 3.32)	0.027
Serotype categories	PCV13 (*n* = 378)	76 (54.5)	302 (245.5)	1		1	
	PPV23non13 (*n* = 367)	38 (10.4)	329 (89.6)	0.46 (0.30, 0.70)	<0.001	0.54 (0.34, 0.86)	0.010
	Non-PPV23 (*n* = 332)	71 (21.4)	261 (78.6)	1.08 (0.75, 1.56)	0.675	1.07 (0.69, 1.65)	0.768
Penicillin	Susceptible (*n* = 284)	120 (21.5)	658 (78.5)	1		1	
	Non-susceptible (*n* = 778)	61 (15.4)[a]	223 (84.6)[b]	1.50 (1.06, 2.12)	0.021	0.91 (0.56, 1.48)	0.907
Cefotaxime	Susceptible (*n* = 127)	151 (23.6)	784 (76.4)	1		1	
	Non-susceptible (*n* = 935)	30 (16.1)[c]	97 (83.9)[d]	1.61 (1.03, 2.51)	0.037	1.38 (0.70, 2.69)	0.350
Influenza vaccination	Not vaccinated (*n* = 652)	114 (17.5)	538 (82.5)	1			
	Vaccinated (*n* = 600)	104 (17.3)	496 (82.7)	0.99 (0.74, 1.33)	0.944		

Abbreviations: IPD, invasive pneumococcal disease; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; PCV13, serotypes included in the 13-valent pneumococcal conjugate vaccine; PPV23non13, additional serotypes included in the 23-valent pneumococcal conjugate vaccine; Non-PPV23, serotypes not included in the 23-valent pneumococcal polysaccharide vaccine and not 6A.
* The model included all variables with a value of $p < 0.20$ in the univariate regression analysis.
[a] Nine strains were resistant.
[b] Thirty-one strains were resistant.
[c] One strain was resistant.
[d] Two strains were resistant.



ST	4	6B	9V	14	18C	19F	23F	1	5	7F	3	6A	19A	2	8	9N	10A	11A	12F	15B	17F	20	22F	33F	6C	23A	24F	13	15A	16F	31	35B	Others
N. deceased	0	2	4	18	1	3	0	0	0	5	32	2	9	1	6	5	4	7	3	2	1	2	6	1	12	7	10	2	8	7	7	7	12
N. alive	10	8	17	61	10	15	5	13	1	19	94	3	46	0	85	31	24	25	70	7	16	6	47	18	32	23	42	3	24	23	32	19	70

Figure 3. Burden of mortality by serotype distribution in patients aged ≥65 years. Catalonia, 2014–2016.
Abbreviations: ST, serotype.

years (adjusted OR 2.91, 95% CI 1.89, 4.48). Meningitis (adjusted OR 2.29, 95% CI 1.25, 4.19) and non-focal bacteraemia (adjusted OR 3.73, 95% CI 2.00, 6.94) remained associated with mortality. High-risk comorbidities were also associated with mortality (adjusted OR 1.89, 95% CI 1.08, 3.32). PPV23non13 serotypes were associated with lower mortality compared with PCV13 serotypes (adjusted OR 0.54, 95% CI 0.34, 0.86).

Of the 219 deaths, 186 (84.9%) were serotyped, and the most frequent serotypes were 3 (17.2%), 14 (9.7%), 6C (6.5%), and 24 F (5.4%) (Figure 3). Of 1034 survivors, 899 were serotyped (86.9%), and the most frequent serotypes were 3 (10.5%), 14 (6.8%), and 6C (3.6%). Significant differences between those who died and those who survived were found for serotypes 3 (17.2% vs. 10.5%; $p < 0.05$), 8 (3.2% vs. 9.5%; $p < 0.05$), and 12F (1.6% vs. 7.8%; $p < 0.05$). In the 126 cases with serotype 3, there were 32 deaths (25.4%).

Discussion

The incidence of IPD decreased slightly in people ≥65 years of age after the introduction of PCV13 in children. There was a decrease in PCV13 serotypes, but an important increase in non-PCV13 serotypes, especially in PPV23non13 serotypes.

Other countries have reported IPD reduction rates ranging from 16% (Regev-Yochay et al., 2017) to 42% (Cabaj et al., 2016; Chalmers et al., 2016), and a greater decrease (65%) in PCV13 serotypes (Regev-Yochay et al., 2017) than those found in the present study. A multicentre European study reported a lower decline in IPD incidence (9%) than in the present study, with large reductions in PCV13 serotypes and an increase in non-PCV13 serotypes (63%) in 2011–2015 compared with 2009 (Hanquet et al., 2018).

In the present study, the most frequent serotype in adults was serotype 3. This serotype represented one of the most frequent serotypes in other age groups since PCV13 was marketed in Catalonia (Ciruela et al., 2018). The lack of PCV13 effectiveness against serotype 3 in children may be the main reason why there was no reduction in its incidence (Domínguez et al., 2017). Other serotypes with high incidences were 8, 14, 12 F, and 22 F (all PPV23 serotypes, except for serotype 14, which is also included in PCV13).

No differences were found in clinical form, ICU admission, and most of the comorbidities between 2009 and 2016, although cases with chronic cardiovascular disease and immunodeficiency decreased and cases with chronic renal disease increased. Sixty-one percent of IPD patients were vaccinated with PPV23, although the majority of them had been vaccinated ≥5 years before. It could be necessary to improve vaccination with PPV23 in older people, mainly those with risk factors for IPD. PPV23 effectiveness against IPD remains unclear (Hanquet et al., 2018; Marrie et al., 2011; Jansen et al., 2009), but it is recommended in persons at risk of IPD and older people (Generalitat de Catalunya, Departament de Salut, 2018). Studies on the effectiveness of PPV23 focusing on specific serotypes and the time of vaccination should be considered. The progressive decline in PCV13 serotypes and the gradual increase in PPV23non13 serotypes suggest that the potential benefits of PCV13 vaccination in adults should be regarded with caution.

During 2014–2016, mortality due to IPD was 17.5%, which is lower than observed in other countries (24–30%) (Harboe et al., 2009; Grau et al., 2016; van Hoek et al., 2012). The difference in mortality may be due, in part, to the characteristics of the population, the type of analysis, and differing serotype distributions.

The study results showed that older age, meningitis or non-focal bacteraemia, high-risk conditions, and IPD caused by PCV13 serotypes were predictive factors of mortality after adjustment for possible confounding factors.

Old age is an independent risk factor for mortality, as described in other studies (Regev-Yochay et al., 2017; Kim et al., 2018; Marrie et al., 2011). This is probably due to reduced immune function (Jansen et al., 2009) and an increase in comorbidities (Yu et al., 2003).

The case fatality rate was higher in people with comorbidities than in healthy people, but only high-risk comorbidities were associated with mortality in the multivariate analysis. Other studies have reported an association between at-risk or high-risk conditions and mortality (Regev-Yochay et al., 2017; Grau et al., 2016), suggesting that the risk condition of the patient plays a decisive role in the outcome of IPD, and not only the biological characteristics of the microorganism, which is in agreement with the present study results. In contrast, other authors (Kim et al., 2018) have found no association with either chronic medical conditions or immunocompromised conditions after the introduction of PCV13 in children. The difference is probably due to the statistical analysis or the characteristics of the populations studied.

The severity of clinical disease was associated with a high risk of mortality. Meningitis and non-focal bacteraemia were associated with mortality. Other authors (Kim et al., 2018) who included referral hospitals found an association with pneumonia, in contrast to our study. These differences may be explained by the fact that 85% of the reports in the present study corresponded to acute hospitals (including secondary and tertiary hospitals).

PCV13 serotypes were independently associated with a higher case fatality rate compared with PPV23non13 serotypes. The most frequent serotypes causing disease in the patients who died were 3, 14, 6C, and 24F, but only serotype 3 was associated with greater mortality, in accordance with other studies (Harboe et al., 2009). Other authors (van Hoek et al., 2012) have found serotypes 19F, 31, and 3 to have the greatest mortality, with similar percentages (41%, 40%, and 39%, respectively). Serotype 3 has been associated with serious disease like empyema (Ciruela et al., 2013b), which could explain, in part, the association with mortality.

This study has some limitations. First, there were some missing clinical data for 2009, the baseline year. However, the analysis of mortality predictors was performed using data from 2014–2016 with higher quality of information. Second, serotype information was missing in 14% of the cases; this limitation was addressed using estimates to calculate the indirect effect of PCV13 in adults.

A strength of this study is the robust data recorded by the MRS, which included more than 85% of acute hospital beds. Another strength is that Catalonia has participated in the European multicentre SpIDnet project (https://sites.google.com/a/epiconcept.fr/ipd-surveillance/home-2) and this has substantially improved the IPD surveillance in our area.

In summary, the incidence of IPD has decreased slightly in people aged ≥65 years due to the impact of childhood PCV13 vaccination although an increase of non-PCV13 serotypes was detected. The case fatality rate was associated with age, meningitis or non-focal bacteraemia, high-risk conditions, and PCV13 serotypes. It is expected that improved PCV13 vaccination coverage in children and an effective PPV23 vaccination strategy in older adults will decrease the incidence and severity of IPD in this age group.

Ongoing surveillance of all microbiological and clinical data is essential to evaluate the preventive measures available.

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Conflict of interest

CMA has received a travel grant from Pfizer. All other authors have no conflicts of interest to declare.

Author contributions

PC made substantial contributions to the data collection process as well as to the conception, design, analysis, and interpretation of data, she drafted and revised the manuscript, gave the final approval of the version to be published, and is the corresponding author. SB conducted the statistical analysis. SB, CI, RP, CMA, SH, IG, AD, and MJ made contributions to the interpretation of the data, provided comments on the draft, and read and approved the final version. The other members of the Working Group contributed to data collection, interpretation of the results, and editing the manuscript.

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