Effectiveness of the 23-Valent Pneumococcal Polysaccharide Vaccine Against Community-Acquired Pneumonia in the General Population Aged ≥60 Years: 3 Years of Follow-up in the CAPAMIS Study

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(See the Major Article by Angoulvant et al on pages 918–24, and the Editorial Commentary by Klugman on pages 925–7.)

Background. The benefits of using the 23-valent pneumococcal polysaccharide vaccine (PPV23) are controversial. This study assessed clinical effectiveness of PPV23 in preventing community-acquired pneumonia (CAP) among the general population aged ≥60 years.

Methods. This was a population-based cohort study involving 27,204 individuals aged ≥60 years in Tarragona, Spain, who were prospectively followed from 1 December 2008 until 30 November 2011. Primary outcomes were hospitalization for pneumococcal CAP (bacteremic and nonbacteremic cases) and all-cause CAP. All CAP cases were radiographically confirmed and validated by checking clinical records. Cox regression was used to evaluate the association between pneumococcal vaccination and the risk of each outcome.

Results. Cohort members were followed for a total of 76,033 person-years (29,065 person-years for vaccinated subjects). Incidence rates (per 1000 person-years) were 0.21 for bacteremic pneumococcal CAP (0.14 vs 0.26 among vaccinated and unvaccinated subjects, respectively), 1.45 for nonbacteremic pneumococcal CAP (1.46 vs 1.44), and 7.51 for all-cause CAP (7.19 vs 7.71). In primary analyses including all cohort members, PPV23 did not appear to be effective against any analyzed outcome. However, a beneficial effect emerged in sensitive and stratified analyses. After multivariable adjustments, as compared with those never vaccinated, recent vaccination with PPV23 (<5 years ago) was associated with reduced risks of bacteremic pneumococcal CAP (hazard ratio [HR], 0.38; 95% confidence interval [CI], .09–1.68), nonbacteremic pneumococcal CAP (HR, 0.52; 95% CI, .29–.92), overall pneumococcal CAP (HR, 0.49; 95% CI, .29–.84), and all-cause CAP (HR, 0.75; 95% CI, .58–.98).

Conclusions. Our data support a protective effect of recent PPV23 vaccination (within previous 5 years) against both pneumococcal and all-cause CAP.

Keywords. elderly; pneumococcal vaccination; pneumonia.

The 23-valent pneumococcal polysaccharide vaccine (PPV23) is currently recommended for high-risk and older adults [1]. There is general consensus about its effectiveness against invasive pneumococcal disease (IPD) [2–5], whereas a possible effect in preventing pneumonia (the most common manifestation of
pneumococcal disease in adults) is more controversial [6–9]. Currently, this is an important issue considering that an alternative vaccine, the pediatric 13-valent pneumococcal conjugate vaccine (PCV13), has also recently been approved for use in adults to prevent IPD and pneumonia [10].

The possible effectiveness of PPV23 against pneumonia is an important concern because IPD events are relatively rare (30–50 cases per 100 000 population-years in older adults) [2, 3], and a possible protective effect against community-acquired pneumonia (CAP) is a key point to assess and compare accurately the cost-effectiveness of different antipneumococcal vaccination strategies.

In the authors’ region (Catalonia, Spain), vaccination with PPV23 has been recommended for people aged ≥60 years since 2002. Considering this, we designed a 3-year prospective cohort study, known as CAPAMIS [11], with the main objective of evaluating clinical benefits from PPV23 use. An interim analysis at 12 months’ follow-up and a summarized research letter have been previously published [12, 13]. This article reports the final results of the CAPAMIS study assessing the clinical effectiveness of PPV23 in preventing CAP (pneumococcal or all-cause), death from CAP, and death from any cause among the general population aged ≥60 years at the end of the 3 years of follow-up.

METHODS

Design, Setting, and Study Population

Study design has been extensively described elsewhere [11]. In brief, this is a closed population-based prospective cohort study including 27 204 individuals aged 60 years or older assigned to 9 primary care centers (PCCs) in the region of Tarragona (Southern Catalonia, Spain), where PPV23 is recommended for persons aged ≥60 years. Cohort members were followed from the start of the study (1 December 2008) until the occurrence of any event, disenrollment from the PCC, death, or the end of the study (30 November 2011). The study was approved by the ethical committee of the Catalanian Health Institute (P09/49) and was conducted in accordance with the general principles for observational studies.

Data Sources

All participating PCCs have a computerized clinical record system that includes administrative data, medical conditions, prescriptions, laboratory results, and diagnosis associated with hospital and outpatient visits. This electronic clinical record system (working since 2000) was used to classify cohort members by their pneumococcal vaccination status as well as to identify comorbidities or underlying conditions and establish baseline characteristics of the cohort at study start. The hospital discharge databases of the 2 reference hospitals in the study area (Joan XXIII and Santa Tecla), coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), were used to identify study events. Besides PCCs’ records, the local civil demographics database (which includes all deaths occurred daily in the study area) was reviewed to identify deaths from any cause occurring among cohort members during the study period.

Outcomes

Primary outcomes were hospitalization for CAP (pneumococcal or all-cause) and death from any cause. Death from CAP was considered when the patient died (in hospital or not) within the first 30 days after CAP diagnosis. Presumptive outcomes were initially identified on the basis of primary (2 first listed) hospital discharge ICD-9 diagnosis codes for pneumonia (480–486). All presumptive cases were further reviewed by 2 trained physician investigators who checked the hospital medical records, only being definitively included if, on conclusion of the medical record review, the diagnosis was verified according to criteria mentioned below.

CAP was defined as an acute respiratory illness, with evidence of the presence of a new infiltrate on a chest radiography. Aspirative pneumonias and nosocomial pneumonias (ie, symptoms occurring >48 hours after hospital admission) were excluded [14]. Bacteremic pneumococcal CAP was considered when Streptococcus pneumoniae was isolated from blood specimens or other sterile sites. Nonbacteremic pneumococcal CAP was considered when the patients had a typical clinical syndrome of pneumonia without bacteremia (negative or not performed blood culture), but they had a sputum culture that yielded pneumococci with no other likely bacterial pathogens and/or had positive Binax-NOW S. pneumoniae urinary antigen test [15].

Conventional diagnostic workup included blood culture, sputum culture, and S. pneumoniae urinary antigen test (Binax-NOW), which were performed as indicated by the attending physician in each case. Pneumococcal isolates were sent for serotyping to the National Center of Microbiology (Madrid, Spain). The investigators who validated clinical data and those who performed microbiological procedures were unaware of the vaccination histories of the subjects.

Exposure

The main explanatory variable was pneumococcal vaccination status. This status was determined by a review of the PCCs’ electronic clinical records, which contain specially designated fields for pneumococcal and influenza vaccinations (virtually all of them are administered at the PCCs in the Spanish health system). At the beginning of the study, cohort members were considered to be immunized against pneumococcus if they had received at least 1 dose of PPV23 in the 5 years before the study started (given that a decline in antibody titers generally occurs at 3–5 years after vaccination) [2, 16]. Subjects were considered to be vaccinated 14 days after vaccine administration. Across the study
period, pneumococcal vaccination status was a time-varying condition as some individuals received PPV23 after study start.

Covariates
Baseline covariates were age, sex, number of outpatient visits to family physician in the 12 months before study start (<3, 3–5, 6–9, ≥10), receipt of influenza vaccine in prior autumn, nursing home residence, history of hospitalization for pneumonia in previous 5 years, presence of chronic pulmonary disease (chronic bronchitis, emphysema, or asthma), coronary artery disease (myocardial infarction or angina), chronic heart disease (congestive heart failure, hypertensive heart disease, cardiomyopathy, valvulopathy, cardiac dilation, or ventricular hypertrophy), history of stroke, hypertension, hypercholesterolemia, obesity, diabetes mellitus, smoking status (never, former, current), alcoholism, chronic severe liver disease (chronic viral hepatitis, alcoholic hepatitis, or cirrhosis), chronic severe nephropathy (nephrotic syndrome, renal failure, dialysis or transplantation), dementia, cancer (solid organ or hematological neoplasia), and immunosuppressive medication (20 mg/day of prednisone or equivalent).

Statistical Analysis
Incidence rates were calculated as person-years, considering in the denominator the sum of the person-time contributed to each individual during the study period. Baseline characteristics according to history of pneumococcal vaccination were compared using \( \chi^2 \) or \( t \) test as appropriate.

To adjust for potential indication bias, we used logistic regression to construct a propensity score that predicted the patient’s likelihood of receiving pneumococcal vaccination at baseline. All above-mentioned covariates were initially considered potential candidates for the calculation of the propensity score. We followed the established recommendations [17–19] to calculate the propensity score. We fit the best model between the model adjusted for propensity score as continuous and divided into quintiles (Supplementary Appendix).

Cox proportional hazards models were used to assess the association between having received the pneumococcal vaccine and the time to the first outcome [20]. We modeled separate analysis. First, we adjusted only for propensity score and the receipt of vaccine. Second, we performed multivariable analysis adjusted for the above-mentioned covariates plus annual influenza vaccination status as a time-varying condition. Age, sex, and influenza vaccine status were judged to be epidemiologically relevant covariates, being included in all the final models. The method to select a subset of covariates to include in the final model was the purposeful selection [20]. We checked for confounders, interactions, and multicollinearity among the independent covariates. The proportional hazard assumptions were assessed by adding the covariate by log-time interactions to the model. Linearity of continuous covariates was tested with fractional polynomials. All models were compared by the partial likelihood ratio test and Akaike information criterion.

We performed stratified analyses by immunological and influenza vaccine status, nursing-home residence when study started, and by subjects receiving PPV23 after study start (who had, theoretically, the highest level of antibody titers and immune protection). In addition, considering that the possible duration of immune and clinical protection after PPV23 has not been well established to date [2, 16], we performed 2 additional sensitivity analyses: (1) classifying as “immunized” all subjects who had received a dose of PPV23 at any time; (2) excluding from the analysis those subjects who had received PPV23 >5 years prior to study start (immunologically heterogeneous group). Statistical significance was set at \( P < 0.05 \) (2-tailed). The analyses were performed using Stata/SE 12.1 (StataCorp).

RESULTS
The 27 204 cohort members were observed for a total of 76 033 person-years, of which 29 065 (38%) person-years corresponded to immunized subjects. At study start, 8981 cohort members were classified into the vaccinated group (PPV23 in prior 5 years), whereas 18 223 were initially classified into the nonvaccinated group (12 044 never vaccinated and 6179 vaccinated >5 years prior). Of the 18 223 subjects initially considered as unvaccinated, 2390 (13%) received PPV23 later (contributing to the analyses with 3472 person-years in the non-vaccinated group and 3597 person-years in the vaccinated group).

The mean age of study subjects when study started was 71.7 years (SD, 8.6 years) and 44.6% were male. Vaccinated subjects were slightly older, had a much higher proportion of influenza vaccination, and had more comorbidities than nonvaccinated subjects (Table 1).

During the study period, 2465 (9.1%) cohort members died and 1444 (5.3%) moved (262, 499, and 683 within the first, second, and third year of follow-up, respectively).

Seven hundred thirteen cohort members were discharged from the reference hospital’s database with an ICD-9 code for pneumonia, but only 566 (79.4%) were validated as CAP cases after clinical records were reviewed (85 were excluded because they did not meet the criteria for pneumonia diagnosis, 10 cases were aspirative pneumonia, 29 were nosocomial pneumonia, and 23 were other diagnosis). Of the 566 cases, blood culture was performed in 369 (65.2%), sputum culture in 278 (49.1%), and pneumococcal urinary antigen test in 460 (81.3%).

Overall incidence rates (per 1000 person-years) were 0.21 (95% confidence interval [CI], 0.13–0.35) for bacteremic pneumococcal CAP (0.14 vs 0.26 among vaccinated and
unvaccinated subjects, respectively), 1.45 (95% CI, 1.20–1.75) for nonbacteremic pneumococcal CAP (1.46 vs 1.44) and 7.51 (95% CI, 6.92–8.16) for all-cause CAP (7.19 vs 7.71).

After propensity adjustments, a protective effect of PPV23 did not appear for bacteremic pneumococcal CAP (hazard ratio [HR], 0.58; 95% CI, .17–2.03), nor for nonbacteremic
pneumococcal CAP (HR, 1.14; 95% CI, .76–1.72) or all-cause CAP (HR, 0.98; 95% CI, .81–1.17). The estimates did not substantially change in multivariable analyses (Table 2).

The all-cause mortality rate was 32.4 per 1000 person-years across the study period (28.4 per 1000 among vaccinated vs 34.9 per 1000 among nonvaccinated subjects; P < .001). Thirty-day case-fatality rates were 13.3% for CAP cases (12.1% among vaccinated and 13.9% among nonvaccinated subjects; P = .532).

After propensity- and multivariable-adjusted analyses, the PPV23 was not associated with a reduction in the risk of death from CAP or all-cause death (Table 2).

Vaccination did not emerge associated with reduced risk of all pneumococcal CAP, all-cause CAP, or death from CAP in stratified analyses focused on immunocompetent or immunocompromised subjects, influenza-vaccinated or nonvaccinated subjects, and nursing home residents. However, in the stratified

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### Table 2. Incidence, Risk of Hospitalization for Community-Acquired Pneumonia, Death From Pneumonia, and All-Cause Death Among Persons Aged ≥60 Years in Relation to Their Pneumococcal Vaccination Status

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Bacteremic Pneumococcal CAP</th>
<th>Nonbacteremic Pneumococcal CAP</th>
<th>All-Cause CAP</th>
<th>Death From CAP</th>
<th>All-Cause Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccinated</td>
<td>4</td>
<td>42</td>
<td>207</td>
<td>27</td>
<td>825</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>12</td>
<td>67</td>
<td>359</td>
<td>48</td>
<td>1640</td>
</tr>
<tr>
<td>Unadjusted incidence rate per 1000 person-years (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccinated</td>
<td>0.14 (.05–.37)</td>
<td>1.46 (1.08–1.97)</td>
<td>7.19 (6.27–8.24)</td>
<td>0.92 (.64–1.35)</td>
<td>28.38 (26.51–30.39)</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>0.26 (.15–.45)</td>
<td>1.44 (1.13–1.83)</td>
<td>7.71 (6.95–8.55)</td>
<td>1.02 (.77–1.36)</td>
<td>34.92 (33.27–36.65)</td>
</tr>
<tr>
<td>Unadjusted HR (95% CI)</td>
<td>0.54 (.17–1.68)</td>
<td>1.04 (.71–1.53)</td>
<td>0.94 (.80–1.12)</td>
<td>0.92 (.58–1.48)</td>
<td>0.81 (.74–.88)</td>
</tr>
<tr>
<td>P Value</td>
<td>.288</td>
<td>.841</td>
<td>.514</td>
<td>.746</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Age- and sex-adjusted HR (95% CI)</td>
<td>0.54 (.17–1.69)</td>
<td>1.09 (.74–1.60)</td>
<td>0.98 (.82–1.16)</td>
<td>1.02 (.64–1.65)</td>
<td>0.90 (.83–.98)</td>
</tr>
<tr>
<td>P Value</td>
<td>.290</td>
<td>.676</td>
<td>.801</td>
<td>.919</td>
<td>.012</td>
</tr>
<tr>
<td>Propensity-adjusted HR (95% CI)</td>
<td>0.58 (.17–2.03)</td>
<td>1.14 (1.76–1.72)</td>
<td>0.98 (.81–1.17)</td>
<td>1.02 (.62–1.68)</td>
<td>0.92 (1–4.00)</td>
</tr>
<tr>
<td>P value</td>
<td>.394</td>
<td>.532</td>
<td>.801</td>
<td>.946</td>
<td>.057</td>
</tr>
<tr>
<td>Multivariable HR ratio (95% CI)</td>
<td>0.57a (.17–1.86)</td>
<td>1.03 (1.69–1.53)</td>
<td>0.95 (.80–1.14)</td>
<td>1.04 (1.64–1.69)</td>
<td>0.97 (1.99–1.05)</td>
</tr>
<tr>
<td>P value</td>
<td>.348</td>
<td>.895</td>
<td>.586</td>
<td>.877</td>
<td>.448</td>
</tr>
</tbody>
</table>

HRs are for vaccinated compared with unvaccinated subjects. Final models were adjusted for epidemiologically relevant, significant, and confounder covariates and interactions as appropriate.

Abbreviations: CAP, community-acquired pneumonia; CI, confidence interval; HR, hazard ratio.

* The 4 cases of bacteremic pneumococcal pneumonia in vaccinated subjects were due to 1 type 6C, 1 type 9N, 1 type 19A, and 1 nontyped. The 12 cases in nonvaccinated subjects were due to 1 each of type 1, type 3, type 4, type 6C, type 7F, type 8, and type 23B; 2 type 22F; and 3 nontyped.

** Of the 109 nonbacteremic pneumococcal pneumonia, blood culture was negative in 74 cases and it was not performed in 35 cases. Overall, 14 cases were diagnosed by positive sputum culture, 5 by positive sputum culture plus urinary antigen test, and 90 by positive urinary antigen test alone. Of the positive sputum cultures for pneumococcus, 7 occurred among vaccinated subjects (1 type 3, 3 type 19A, 1 type 29, 1 type 35F, and 1 nontyped), whereas 12 occurred among nonvaccinated subjects (3 type 3; 1 each of type 6A, 16F, 19A, 19F, and 22F; 2 type 35B, and 2 nontyped).

† Fifty-eight of the 666 patients suffered ≥1 episode of CAP throughout the 3-year survey period (44 had 2 episodes, 12 had 3 episodes, 1 had 4 episodes, and 1 had 5 episodes). Of these 58 patients, 10 were never vaccinated, 23 had received the 23-valent pneumococcal polysaccharide vaccine (PPV23) within 5 years before study start, and 25 patients had received PPV23 >5 years before study start.

‡ Model adjusted for propensity score in quintiles.

§ Adjusted for age, sex, influenza vaccine status, nursing home residence, cancer, immuno-suppressive medication, smoking as confounder, chronic pulmonary disease, diabetes, and immunodeficiency.

¶ Adjusted for age, sex, influenza vaccine status, visits in prior 12 months, nursing home residence, history of prior pneumonia, history of stroke, chronic pulmonary disease, obesity, hypertension, and smoking as confounder.

‖ Adjusted for age, sex, influenza vaccine status, visits in prior 12 months, nursing home residence, history of prior pneumonia, history of coronary artery disease, history of stroke, chronic pulmonary disease, chronic heart disease, chronic nephropathy, diabetes, smoking, immuno-suppressive medication, and interactions terms for history of prior pneumonia*chronic pulmonary disease, sex*immuno-suppressive medication, and chronic nephropathy*history of stroke, chronic heart disease, immuno-suppressive medication). Asterisks indicate “interaction between.”

• Adjusted for age, sex, influenza vaccine status, nursing home residence, and history of prior pneumonia.

– Adjusted for age, sex, influenza vaccine status, number of outpatient visits in previous 12 months, nursing home residence, history of prior pneumonia, history of coronary artery disease, history of stroke, chronic heart disease, chronic pulmonary disease, chronic liver disease, chronic nephropathy, diabetes, hypertension, hypercholesterolemia, obesity, smoking, cancer, immunodeficiency, dementia, immuno-suppressive medication, and interactions terms for sex*age, sex*dementia, history of prior pneumonia*hypercholesterolemia, history of coronary artery disease*chronic heart disease, chronic liver disease*cancer, chronic nephropathy*cancer, cancer*dementia, nursing-home residence*log (time), cancer*log (time), and dementia*log (time).
analysis, which focused on the 2390 cohort members vaccinated after study start, PPV23 was shown to be significantly associated with a considerable risk reduction of all pneumococcal CAP (HR, 0.09; 95% CI, 0.02–0.48; \( P = .004 \)) and an almost significant reduction in the risk of all-cause CAP (HR, 0.53; 95% CI, 0.26–1.08; \( P = .079 \)) in these subjects (Table 3).

### Table 3. Stratified Analyses on Pneumococcal Vaccine Effectiveness

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>Immune Status</th>
<th>Influenza Vaccine Status</th>
<th>Nursing Home Residence</th>
<th>PPV23 After Study Start</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Competent ( n = 24,278 )</td>
<td>Compromised ( n = 29,296 )</td>
<td>Vaccinated ( n = 14,368 )</td>
<td>Unvaccinated ( n = 12,836 )</td>
</tr>
<tr>
<td>Pneumococcal CAP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>97</td>
<td>28</td>
<td>81</td>
<td>44</td>
</tr>
<tr>
<td>Multivariable HR</td>
<td>0.93</td>
<td>1.13</td>
<td>1.32</td>
<td>0.56</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(.60–1.42)</td>
<td>(.50–2.54)</td>
<td>(.84–2.07)</td>
<td>(.24–1.30)</td>
</tr>
<tr>
<td>( P ) Value</td>
<td>.722</td>
<td>.769</td>
<td>.237</td>
<td>.177</td>
</tr>
<tr>
<td>All-cause CAP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>444</td>
<td>122</td>
<td>348</td>
<td>218</td>
</tr>
<tr>
<td>Multivariable HR</td>
<td>0.89</td>
<td>1.27</td>
<td>0.97</td>
<td>1.02</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(.72–1.09)</td>
<td>(.97–1.86)</td>
<td>(.78–1.21)</td>
<td>(.73–1.41)</td>
</tr>
<tr>
<td>( P ) Value</td>
<td>.240</td>
<td>.221</td>
<td>.804</td>
<td>.926</td>
</tr>
<tr>
<td>Death from CAP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>56</td>
<td>19</td>
<td>47</td>
<td>28</td>
</tr>
<tr>
<td>Multivariable HR</td>
<td>1.01</td>
<td>1.25</td>
<td>1.00</td>
<td>1.28</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(.57–1.77)</td>
<td>(.48–3.26)</td>
<td>(.55–1.81)</td>
<td>(.53–3.10)</td>
</tr>
<tr>
<td>( P ) value</td>
<td>.977</td>
<td>.653</td>
<td>.995</td>
<td>.581</td>
</tr>
</tbody>
</table>

The HRs are for vaccinated subjects compared with nonvaccinated subjects and were adjusted for age, sex, influenza vaccination status, number of outpatient visits in previous 12 months, nursing home residence, history of prior pneumonia, coronary artery disease, cerebrovascular disease, chronic pulmonary disease, chronic heart disease, chronic liver disease, chronic nephropathy, diabetes, cancer, immunodeficiency, dementia, hypertension, hypercholesterolemia, obesity, alcoholism, smoking, and immunosuppressive medication.

Abbreviations: CAP, community-acquired pneumonia; CI, confidence interval; HR, hazard ratio; PPV23, 23-valent pneumococcal polysaccharide vaccine.

### Table 4. Sensitivity Analysis on Pneumococcal Vaccine Effectiveness, Reclassifying as Immunized All Subjects Vaccinated at Any Time

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Bacteremic Pneumococcal CAP ( n = 12 )</th>
<th>Nonbacteremic Pneumococcal CAP ( n = 101 )</th>
<th>Overall Pneumococcal CAP ( n = 113 )</th>
<th>All-Cause CAP ( n = 515 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted HR</td>
<td>1.27</td>
<td>1.75</td>
<td>1.69</td>
<td>1.74</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(.38–4.23)</td>
<td>(1.13–2.72)</td>
<td>(1.12–2.55)</td>
<td>(1.44–2.12)</td>
</tr>
<tr>
<td>( P ) Value</td>
<td>.693</td>
<td>.013</td>
<td>.013</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age- and sex-adjusted HR</td>
<td>0.98</td>
<td>1.15</td>
<td>1.12</td>
<td>1.18</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(.28–3.43)</td>
<td>(.73–1.78)</td>
<td>(.74–1.72)</td>
<td>(.96–1.44)</td>
</tr>
<tr>
<td>( P ) Value</td>
<td>.980</td>
<td>.567</td>
<td>.591</td>
<td>.114</td>
</tr>
<tr>
<td>Multivariable HR</td>
<td>0.47(^a)</td>
<td>0.71(^b)</td>
<td>0.68(^c)</td>
<td>0.92(^d)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(.09–2.45)</td>
<td>(.39–1.27)</td>
<td>(.39–1.18)</td>
<td>(.71–1.20)</td>
</tr>
<tr>
<td>( P ) Value</td>
<td>.373</td>
<td>.242</td>
<td>.172</td>
<td>.550</td>
</tr>
</tbody>
</table>

This analysis included a total of 24,814 subjects (15,125 vaccinated at any time vs 9,689 unvaccinated at study start) and excluded the 2390 cohort members who received 23-valent pneumococcal polysaccharide vaccine after the study started (2355 prime vaccinated and 35 revaccinated). Final models were adjusted for epidemiologically relevant and significant covariates.

Abbreviations: CAP, community-acquired pneumonia; CI, confidence interval; HR, hazard ratio.

\(^{a}\) Adjusted for age, sex, influenza vaccination, chronic pulmonary disease, diabetes, immunodeficiency, cancer, and immunosuppressive medication.

\(^{b}\) Adjusted for age, sex, influenza vaccination, number of outpatient visits, nursing home residence, history of prior pneumonia, stroke, chronic pulmonary disease, chronic heart disease, and smoking.

\(^{c}\) Adjusted for age, sex, influenza vaccination, number of outpatient visits, nursing home residence, history of prior pneumonia, stroke, chronic pulmonary disease, chronic heart disease, diabetes, and smoking.

\(^{d}\) Adjusted for age, sex, influenza vaccination, number of outpatient visits, nursing home residence, history of prior pneumonia, stroke, chronic pulmonary disease, chronic heart disease, chronic nephropathy, liver disease, smoking, and immunosuppressive medication.
In the analysis classifying as “immunized” all cohort members who had received PPV23 at any time, a protective effect of vaccination did not appear for any analyzed outcome (Table 4). Finally, in the analysis excluding 6179 cohort members who had received PPV23 >5 years before study start, a beneficial effect of vaccination emerged among the remaining 21 025 cohort members. After multivariable adjustments, compared with nonvaccination, recent vaccination with PPV23 (<5 years ago) was associated with reduced risks of bacteremic pneumococcal CAP (HR, 0.38; 95% CI, 0.09–1.68), nonbacteremic pneumococcal CAP (HR, 0.52; 95% CI, 0.29–0.92), overall pneumococcal CAP (HR, 0.49; 95% CI, 0.29–0.84), and all-cause CAP (HR, 0.75; 95% CI, 0.58–0.98) (Table 5).

**DISCUSSION**

Clinical effectiveness of PPV23 is controversial. In fact, the 2 last published meta-analyses (a Cochrane Collaboration and a World Health Organization–commissioned meta-analysis) reported contradictory conclusions (in favor and against vaccine effectiveness, respectively) [5, 6].

In the present study, the vaccine was apparently ineffective when considering the whole study population, but was shown to be significantly effective in subgroup analysis focused on subjects more recently vaccinated (<5 years before or after the study started), which illustrates why the >10 meta-analyses published to date [4–6, 21–28] evaluating this issue have had difficulty in reaching a clear conclusion. Because protective effects against IPD have been reported in several case-control studies and severe adverse reactions are a rare event after immunization, PPV23 is recommended given the acceptable risk/benefit ratio (even considering a possible null effect against pneumonia) [1].

The last Cochrane meta-analysis judged a vaccine efficacy of 74% (54%–85%) against IPD (basically bacteremic pneumococcal pneumonia), but it concluded that there was not compelling evidence to demonstrate a protective effect against overall pneumonia (odds ratio, 0.71; 95% CI, 0.52–0.97) [5]. Our data focused on cohort members who received PPV23 after study start.
(which shows a significant vaccination effectiveness against pneumococcal pneumonia and an almost significant effect against all-cause CAP), together with data focused on people receiving PPV23 in the 5 years before the study start (which shows a significant vaccine effectiveness, as compared with never vaccinated, of 51% [95% CI, 16%–71%] against overall pneumococcal CAP and 25% [95% CI, 2%–42%] against all-cause CAP), do not disagree with data reported in the abovementioned Cochrane meta-analysis and supports the benefit of PPV23 in preventing pneumonia.

Our findings agree with those of a prior cohort study in the same geographical area, where a vaccine effectiveness of 45% (12%–66%) against pneumococcal CAP and 21% (2%–36%) against all-cause CAP was observed during 2002–2005 among elderly people (mean age, 74.5 years) who had received PPV23 within the previous 2 years [29]. Our data also fit with a recent randomized controlled trial and a large case-control study that have reported significant protective effects of PPV23 against pneumococcal and all-cause pneumonia among nursing home residents and community-dwelling individuals, respectively [8, 9].

We note, however, that these findings must be interpreted with caution because they only appeared in subgroup analysis; the size of subgroups was reduced in some cases (ie, individuals vaccinated after study start); the number of cases was low for some events; and, especially for all-cause CAP, the statistical significance was only marginal.

According to the literature, the duration of immunity after receipt of PPV23 is not always homogeneous in all individuals [2, 16]. Because specific antibody titers decline 3–5 years after PPV23 (and revaccination is recommended at 5 years for people aged <65 years) [1, 2], in our primary analyses we classified as nonimmunized those subjects who had received PPV23 >5 years prior to study start. Some of these individuals could have a certain degree of protection that was not considered in the primary analysis. We explored possible bias in sensitivity analysis, classifying as immunized all subjects receiving PPV23 at any time (the results of which did not substantially differ with primary analysis), but possible misclassification cannot be fully excluded considering the lack of immunologic laboratory data (ie, specific antibody titers and their functional activity) among the study cohort. Indeed, although PPV23 did not seem to be significantly associated with any protective effect when all cohort members were included in the analyses (independent of time since vaccination), the vaccine proved to be significantly effective against overall pneumococcal CAP (including nonbacteremic cases) and all-cause CAP when the subgroup of subjects who had received PPV23 >5 years prior to study start were excluded from the analysis. Our data suggest that these individuals are an immunologically heterogeneous group that may obscure possible protective effects of vaccination, either if they are considered immunized (as a big effect cannot be expected) or if they are considered nonimmunized (as some individuals may have a certain degree of antibody persistence and protection).

A major strength of this study is that it was population-based and included all target populations for pneumococcal vaccination in a well-defined geographical area. Other strengths were the prospective design, the validation of outcome events by checking clinical records that protected against biases related to recall, and the use of survival analysis methods to estimate vaccine effectiveness adjusted by propensity score for pneumococcal vaccination as well as important covariates such as age, influenza vaccination status, and major underlying conditions in the multivariable analyses. Main limitations are inherent with its observational nature and nonrandomized design. The study was underpowered to assess uncommon events such as bacteremic pneumococcal CAP, and we were unable to assess the overall burden of CAP as only hospitalized patients were included.

Given the large size of the study population, many statistically significant differences appear when comparing vaccinated and unvaccinated groups, but most of them were not substantial. The authors performed multivariable adjustment for potential confounders, along with additional adjustment for the propensity score to account for these differences in the statistical analysis. However, as with all observational studies, a residual confounding for unobserved factors cannot be completely excluded.

The rate of influenza vaccination was considerably different between those receiving and not receiving pneumococcal vaccine. This is not surprising given the programmatic approach taken to administer both vaccines together. However, because influenza vaccine exposure could affect study events, to explore possible confounding we did supplementary analyses on PPV23’s effectiveness according to cohort members who had received, or not received, the influenza vaccine when the study started. We did not observe any significant protective effect of PPV23 in both subgroups, which suggests that there was non important confounding due to influenza vaccination.

In conclusion, apart from a protective effect against pneumococcal CAP (which has relatively low incidence), our data support the finding that PPV23 provides a moderate benefit against overall CAP among the general population aged ≥60 years. Our data showing clinical benefits for cohort members recently vaccinated (but not for those receiving PPV23 >5 years prior) suggests that clinical protection wanes after 5 years and supports the need for revaccination. Nevertheless, considering the limited degree and duration of clinical protection provided by the PPV23, more effective antipneumococcal vaccination strategies (eg, also using the new PCV13 or future protein-based vaccines with serotype-independent protection) [30, 31] are needed.
Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the authors that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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