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The effectiveness of the polysaccharide pneumococcal vaccine for the prevention of hospitalizations due to *Streptococcus pneumoniae* community-acquired pneumonia in the elderly differs between the sexes: Results from the Community-Acquired Pneumonia Organization (CAPO) international cohort study

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ABSTRACT

Background: The effectiveness of the 23-valent pneumococcal polysaccharide vaccine (PPV23) to prevent hospitalizations due to *Streptococcus pneumoniae* community-acquired pneumonia (SpCAP) is controversial. Recent literature suggests that vaccine effectiveness may be influenced by sex. In this study, we define the effectiveness of prior PPV23 vaccination for the prevention of hospitalizations due to SpCAP, and evaluate the impact of sex on this effectiveness.
Methods: This was a nested case–control study from the CAPO international cohort study database. SpCAP was defined as CAP plus *S. pneumoniae* identified in blood, bronchoalveolar lavage, sputum, or urinary antigen. Vaccination with PPV23 prior to hospitalization was defined as documented in the medical record. A propensity score-weighted logistic regression model was used to calculate odds ratios. The adjusted vaccine effectiveness (aVE) was calculated as 1-adjusted odds ratio.
Results: From a total of 2688 elderly adult hospitalized patients with CAP, SpCAP was identified in 279 (10%). The overall aVE was 37% (95% CI: 10.1–55.4%, $P = 0.01$). For males, the aVE was 34% (95% CI: −1.0% to 57.3%, $P = 0.06$). For females the aVE was 68% (95% CI: 40.3–83.0%, $P = 0.001$).
Conclusions: PPV23 protects elderly patients from hospitalization due to SpCAP, but female sex drives the effectiveness. Future analysis of vaccine trials should consider the importance of sex as a stratification factor.

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1. Introduction

Community-acquired pneumonia (CAP) is a leading cause of infectious diseases-related deaths worldwide [1]. The primary pathogen causing CAP is *Streptococcus pneumoniae* [2]. Deaths due to *Streptococcus pneumoniae* community-acquired (SpCAP) are most pronounced in the elderly population, and therefore it is critical to ensure this population is vaccinated [2]. Prior to 2012, only one vaccine, the 23-valent polysaccharide pneumococcal vaccine (PPV23), was licensed to protect the elderly population from SpCAP. It is estimated that up to two thirds of the healthy elderly population in the United States has received this vaccine [3–5]. Controversy still exists regarding the level and type of protection that the PPV23 offers to the elderly population. Whether the PPV23 is effective for the prevention of SpCAP has been questioned [6]. There are, however, studies illustrating that the PPV23 vaccine prevents development of the most severe forms of pneumonia, decreasing the need for hospitalization in the elderly [7,8].

Whether the efficacy of the PPV23 differs between males and females has not been reported. There are several reports of immune responses and adverse reactions to viral and bacterial vaccines differing between males and females [9,10]. Females, including those from elderly populations, are more likely to report adverse reactions to vaccines than their male counterparts [9]. Higher antibody responses are also reported in females compared with males, which is assumed to suggest that protection against infection might be higher in females as well [11].

The Community-Acquired Pneumonia Organization (CAPO) cohort study is a multicenter, international study of adult hospitalized patients with CAP, which began in 2001. The database for the CAPO study contains information on over 7000 patients with CAP. For patients aged 65 or older, data have been collected regarding pneumococcal vaccine status prior to hospitalization. Our teams' access to this unique dataset provided us the opportunity to evaluate the role of pneumococcal vaccination in the elderly. The primary objectives of this study were: (1) to define the effectiveness of prior PPV23 vaccination for the prevention of hospitalizations due to SpCAP in the elderly, and (2) to determine if the effectiveness of the PPV23 for the prevention of hospitalizations due to SpCAP differs between elderly males and females.

2. Methods

2.1. Study design and population

This was a nested case–control study of the CAPO international cohort study database [12]. Data were collected from January 1, 2001 to August 20, 2012. In each participating center, medical records of hospitalized patients with the diagnosis of CAP were reviewed. Charts were selected among all patients diagnosed with CAP at each respective institution. Investigators completed a case report form, which was transferred via a secure website to the University of Louisville Clinical and Translational Research Support Unit (CTRSU) located in the Division of Infectious Diseases at the University of Louisville. A sample of the data collection form is available at: www.caposite.com. Validation of data quality was performed at the CTRSU before the case was entered in the CAPO database. This included a review of each case by a member of the CTRSU. Any issues with respect to the case (e.g. out of range values, missing data, and data that was clinically questionable) were referred back to the investigator who had entered the data. Once all queries were fixed, the case was accepted into the database for analysis.

All subjects aged 65 and older entered into the CAPO database from the USA and Europe were included in the current analysis. Patients with HIV infection were excluded. Each analysis was performed three times, once for the overall population, once for males only, and once for females only.

2.2. Human subjects protection

Institutional Review Board approval was obtained at all participating CAPO institutions prior to data collection.

2.3. Study definitions

Community-Acquired Pneumonia (*CAP*) – CAP was defined as a new pulmonary infiltrate (within 24 h of admission), associated with at least one of the following factors: a new or increased cough, an abnormal temperature (<35.8 °C or >37.8 °C), or an abnormal leukocyte count (leukocytosis, leukopenia or the presence of immature neutrophils). Pneumonia was considered as community-acquired if a patient had no history of hospitalization during the two weeks prior to admission.

S. pneumoniae community-acquired pneumonia (*SpCAP*) – SpCAP was defined as the presence of CAP plus identification of *S. pneumoniae* from blood, bronchoalveolar lavage, sputum, or urinary antigen. Patients with SpCAP were considered "cases" for the nested case–control study.

Prior PPV23 vaccination – A patient was defined as being vaccinated with the PPV23 prior to hospitalization due to CAP if it was documented in the medical record.

The primary predictor variable in our analyses was prior PPV23 vaccination, as documented in the medical record. Patients without documentation of vaccination were considered not vaccinated.

The outcome variable for our study was the etiology of CAP, defined as *S. pneumoniae* (cases) versus any other etiology/unknown etiology (controls).

We included the following confounding variables in our analysis: age, season, comorbidities (COPD, diabetes, congestive heart failure, liver disease, renal disease), and history of a cerebrovascular accident, history of cancer, history of CAP admission in the prior year, nursing home residence, and an indicator variable for region (USA versus Europe).

2.4. Statistical analysis

Baseline patient characteristics between elderly patients with a history of PPV23 vaccination and those without vaccination were compared using Chi-squared or Fisher's Exact tests for categorical variables and the Mann–Whitney *U*-test for continuous variables. The same characteristics were compared between elderly males and females with a history PPV23 using the same methods.

To examine the effectiveness of the PPV23 in preventing hospitalizations due to *S. pneumoniae*, a test-negative design was used [13]. Cases were considered patients with *S. pneumoniae*, while controls were considered patients without *S. pneumoniae* identified in any clinical sample. To evaluate the adjusted vaccine effectiveness, we used a weighted propensity score analysis. The propensity score was created using a logistic regression model with vaccination status as the outcome and age, season, the comorbidities and patient history variables listed previously, and region as independent variables. Age was modeled using a restricted cubic spline with four knots, as it was not assumed age would linearly predict vaccination status. The predicted probabilities from this model (e.g. the propensity score) were used as a covariate in a final weighted logistic regression model. The model created using the *svydesign* function from the *survey* package in the R statistical software v 2.15.1 [14].

This final propensity-weighted model provided odds ratios, *P*-values, and 95% confidence intervals. The vaccine effectiveness was calculated as one minus the adjusted odds ratio, with 95%