Bacteremic Pneumonia before and after Withdrawal of 13-Valent Pneumococcal Conjugate Vaccine from a Public Vaccination Program in Spain: A Case-Control Study

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Objective To compare the incidence and epidemiology of bacteremic community-acquired pneumonia (CAP) in the setting of changes in 13-valent pneumococcal conjugate vaccine (PCV13) coverage.

Study design In the region of Madrid, universal immunization with the PCV13 started in May 2010. In July 2012, public funding ceased. Vaccination coverage decreased from >95% to 82% in 2013 and to 67% in 2014. We performed a multicenter surveillance and case-control study from 2009-2014. Cases were hospitalized children with bacteremic CAP. Controls were children selected 1:1 from next-admitted with negative blood cultures and typical, presumed bacterial CAP.

Results Annual incidence of bacteremic CAP declined from 7.9/100 000 children (95% CI 5.1-11.1) in 2009 to 2.1/100 000 children (95% CI 1.1-4.1) in 2012. In 2014, 2 years after PCV13 was withdrawn from the universal vaccination program, the incidence of bacteremic CAP increased to 5.4/100 000 children (95% CI 3.5-8.4). We enrolled 113 cases and 113 controls. *Streptococcus pneumoniae* caused most of bloodstream infections (78%). Empyema was associated with bacteremia ($P = .003$, OR 3.6; 95% CI 1.4-8.9). Simple parapneumonic effusion was not associated with bacteremia. Incomplete PCV immunization was not a risk factor for bacteremic pneumonia.

Conclusions High rate of PCV13 immunization was associated with decreased incidence of bacteremic CAP; this incidence increased when rate of immunization fell. Empyema (but not parapneumonic pleural effusion) was associated with bacteremia. *(J Pediatr 2016;171:111-5)*.

Streptococcus pneumoniae is the main etiologic agent of bacterial community-acquired pneumonia (CAP).[1] The Madrid region historically funded vaccine administration for 7-valent pneumococcal conjugate vaccine (PCV7) and subsequently 13-valent pneumococcal conjugate vaccine (PCV13), resulting in >95% vaccine coverage. In July 2012, PCV13 was withdrawn from the universal vaccination program and PCV13 became an out-of-pocket expenditure. Coverage dropped to 82% in 2013, and 67% in 2014.[2]

CAP is associated with bloodstream infection in approximately 7%-15% of children.[1-4] Bacteremic pneumonia accounts for one-third to one-half of invasive pneumococcal disease (IPD). Observational studies have shown a decrease of IPD incidence after PCV13 implementation.[5] We hypothesized that bacteremic CAP would increase after public fundinwas removed because of the drop in vaccine coverage. Our aims were to compare the incidence and epidemiology of bacteremic CAP in the setting of changes in PCV13 coverage.

Methods

This industry-independent, collaborative, multicenter, and epidemiologic case-control study is nested in a broader bacteremia surveillance study called the Bacteremia in Children Observation Program. Twelve of 25 public pediatric hospitals in Madrid participated in the study. Eight were secondary centers, and 4 were tertiary centers (**Table I**; available at www.jpeds.com). Pediatric population covered by the participating centers was 38.4% of the total pediatric population. Population sizes were obtained from official reports of

CAP	Community-acquired pneumonia
IPD	Invasive pneumococcal disease
PCV13	13-valent pneumococcal conjugate vaccine
PCV7	7-valent pneumococcal conjugate vaccine
WBC	White blood cell

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Madrid Health Government. The Institutional Ethical Board of Hospital La Paz approved the Bacteremia in Children Observation Program (code PI-1679).

We enrolled all patients with bacteremic CAP <14 years old and admitted to any of the participating hospitals from January 1, 2009 to June 1, 2014. Bacteremic CAP was defined as cough, fever >38°C, consolidation reported by a senior radiologist, and positive blood culture for a significant pathogen. All children hospitalized for CAP during the study period had blood cultures obtained and blood for biomarkers at presentation.

Significant bacteremia was defined as those caused by *S pneumoniae*, *Haemophilus influenzae*, *Streptococcus pyogenes*, *Moraxella catarrhalis*, *Salmonella* sp., *Staphylococcus aureus*, and any other bacterium considered clinically relevant. All positive blood cultures were obtained from the microbiology laboratory database of each center. Coagulase-negative cocci and group viridans *Streptococcus* were identified as contaminants. Suspected cross-contamination and duplicated cultures were excluded. Blood was cultured using the BacT/ALERT 3D blood culture system (bioMérieux, Marcy L'Etoile, France) or BacTec 9240 blood culture system (Becton Dickinson and Co, Franklin Lakes, New Jersey). *S pneumoniae* isolates were identified on the basis of colony morphology, Gram stain, catalase test, and optochin susceptibility. Strains were sent to the Madrid Regional Public Health Laboratory where serogroups/serotypes were determined using a combination of latex agglutination (Pneumotest-Latex kit; Statens Serum Institut, Copenhagen, Denmark) and Quellung reaction with factor antisera (Statens Serum Institut).

Selection of Control Subjects

The control group consisted of next patients with typical bacterial pneumonia without bacteremia who were admitted immediately after a patient with bacteremia was included. They were matched (1:1) on a monthly basis. Typical bacterial CAP was defined as cough, axillary temperature ≥38°C, consolidation reported by a senior radiologist, biochemical/microbiologic criteria for presumptive bacterial etiology, and the need for a full course of antibiotic therapy according to the attending physician. Criteria for presumptive bacterial etiology were either a positive culture in pleural fluid, or high biomarker levels and elevated white blood cell (WBC) count. Elevation of biomarkers and WBCs was defined as C-reactive protein >80 mg/L or procalcitonin >2 ng/mL, and WBCs $>15 \times 10^9$/L. These criteria were obtained from Van den Bruel's 2011 systematic review.[6]

Exclusion Criteria

Exclusion criteria were known immunodeficiency, cystic fibrosis, nosocomial pneumonia, blood cultures obtained from a central line, and unclassified or atypical CAP. Cases of unclassified or atypical CAP were those not meeting inclusion criteria. CAP with a positive serology (IgM+ or IgG 4-fold increase) for *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, or *Legionella pneumophila* were excluded. Patients with CAP also were excluded if they had a rapid antigen detection test positive for respiratory syncytial virus. Children with asthma and children born premature were not excluded.

Data Collection

Data were collected from July 2014 to February 2015. We surveyed the medical records of the patients, and data were gathered into a confidential, unique database. Baseline features, laboratory values, and immunization data were recorded. Exclusively, the principal investigator and a biostatistician handled the database.

Variables

We studied potential risk factors associated with bacteremia: age group (<2 years, ≥2 years), male sex, vaccination status, fever at admission (≥39°C, ≥40°C), underlying disease, and parapneumonic pleural effusion and empyema (both confirmed by ultrasonography) (**Table II**; available at www.jpeds.com). WBC count, neutrophil count, and C-reactive protein were not analyzed to avoid bias, and inclusion criteria for controls included these factors.

Statistical Analyses

Incidence rates are presented as incidence with 95% CIs. Categorical variables are presented with frequency distributions. Descriptive statistics of the continuous variables are provided for both the clinical and laboratory variables. Number of subjects, mean ± SD is provided. For the incidence calculation, numerator was the number of annual bacteremia and denominator was the population attended in the participating hospitals (417 210 children).

In order to assess the differences in the categorical variables, we employed a χ^2 test or Fisher exact test if there were ≤5 items of data in a cell. All statistical tests were 2-sided. All P values of <.05 were considered significant. OR with 95% CIs was used to assess association of bacteremia with outcome variables. Vaccine effectiveness was calculated with the formula $(1 - \text{OR}) \times 100$, according to standard recommendations for case-control studies.[7]

We performed both univariate and multivariate logistic regression analysis. In order to assess independent risk factors for bacteremia, we included all variables associated with an increased likelihood of bacteremia in the univariate analysis. A significance level of 0.25 was used for including variables in the multivariate, conditional logistic regression model. An introductory procedure was employed. The statistical analysis was performed with IBM SPSS Statistics for Windows, Version 19.0 (IBM Inc, Armonk, New York).

Results

All 113 patients recorded with bacteremic pneumonia were allocated to the case group. Two hundred eighty-six patients with CAP admitted were considered for the control group. A total of 168 (58%) patients were excluded, as they did not fulfill the criteria for typical bacterial pneumonia. As a result, 118 (42%) patients were eligible. Five (4% of 118) were