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Clinical features of adults with seven-valent-conjugated-vaccine-serotype pneumococcal pneumonia

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ABSTRACT

Background: Despite the reduction in adult invasive pneumococcal disease through 'herd protection' consequent to the introduction of childhood pneumococcal conjugate vaccination (PCV), a significant proportion of adults continue to develop pneumococcal pneumonia caused by one of the seven serotypes included in the seven-valent conjugated pneumococcal vaccine (PCV7). The clinical features and outcomes of these adults have not been previously reported.
Methods: Adults recruited over a three year period to a large prospective cohort study of community acquired pneumonia (CAP) were investigated for pneumococcal serotypes using a validated multiplex immunoassay (Bio-plex). The baseline characteristics and outcomes of adults with PCV7-serotype CAP in comparison to those with non-PCV7-serotype CAP were established.
Results: Pneumococcal aetiology was identified in 415 of 1166 (35.6%) individuals, and a serotype determined in 287 (69.2%). Following exclusion of three individuals with both a PCV7 and non-PCV7 serotype, 77 of the remaining 284 (27.1%) adults had CAP due to PCV7 serotypes. Adults with PCV7-serotype CAP were older (median years (inter-quartile range) 73.3 (60.8–84.4) versus 65.0 (46.1–78.0); $p = 0.001$) and were more likely to have a World Health Organisation performance status ≥ 1 (odds ratio (OR) 2.05, 95% confidence interval (CI) 1.21–3.50).The presence of stroke (adjusted OR 2.84, 95% CI 1.36–5.95) and dementia (adjusted OR 3.55, 95% CI 1.26–9.94) as underlying co-morbid illnesses were independently associated with PCV7-serotype CAP; 30-day mortality was significantly greater in adults with PCV7-serotype CAP (adjusted OR 4.38, 95% CI 1.85–10.34).
Conclusion: A significant proportion of adults continue to develop PCV7-serotype CAP in the era of childhood pneumococcal conjugate vaccination. These adults are more likely to have stroke and dementia as underlying co-morbid illnesses, and have a higher 30-day mortality. A combination of pneumococcal transmission factors, host factors and pneumococcal serotype specific characteristics are likely to explain these findings.

1. Introduction

Streptococcus pneumoniae remains the leading microbial aetiology of community acquired pneumonia (CAP) in adults requiring hospital admission [1,2]. It is estimated that there over 400,000 admissions in the U.S. due to pneumococcal pneumonia [3] and UK estimates report over 45,000 admissions attributable to pneumococcal disease, annually [4]. The associated mortality is 7–17%, but considerably higher for older age groups [1,4,5]. Increasing age and co-morbidity are recognised risk factors for pneumococcal CAP [6–8], and admissions are predicted to increase by 96% in the next few decades due to an aging population [9]. To date, over 90 different pneumococcal serotypes have been identified.

PCV7 was introduced to the UK and US child immunisation schedules in 2006 and 2000 respectively, followed by a 13-valent conjugated pneumococcal vaccine (PCV13) in 2010 in both countries. Consequent to the introduction of PCV, a decline in invasive pneumococcal disease (IPD) due to vaccine-type serotypes was seen in children [10,11]; an effect that has also been translated to adults through 'herd protection' [10,12,13]. However, even in the post-vaccine era, as much as 35% of pneumococcal pneumonia in adults is caused by PCV7 serotypes [10,12,14]. The clinical features of these adults who continue to develop PCV7-serotype disease have not been characterised adequately. Studies of IPD comparing PCV7 serotypes to non-PCV7 serotypes have found variable differences in mortality and the presence of comorbid illness between

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the two groups [15,16]. There are no data regarding non-invasive PCV7-serotype CAP in this regard.

We investigated a large prospective cohort of pneumococcal CAP to characterise the baseline characteristics of adults who were hospitalised with PCV7-serotype CAP, and to establish whether these patients had different clinical outcomes in comparison to adults with non-PCV7-serotype CAP.

2. Methods

An observational prospective cohort study was conducted between September 2008 and September 2011, at two large teaching hospitals in the UK. Consecutive adults (aged over 16 years) admitted with CAP were identified from acute admission units and wards on a daily basis. CAP was defined as (1) the presence of symptoms consistent with acute lower respiratory tract infection (at least one of increasing breathlessness, cough, sputum or fever) and (2) the presence of a new infiltrate on the chest radiograph. Exclusion criteria were post obstruction pneumonia due to lung cancer, discharge from hospital in the 10 days prior to admission or tuberculosis. Following informed consent, data regarding patient demographics, baseline World Health Organisation (WHO) performance status, underlying co-morbid illnesses, radiological findings, microbiological investigations and outcome measures were recorded on a standardised proforma [17]. If adults were unable to provide consent, informed assent was obtained from a relative. The local hospital patient information system, which routinely captures data related to death (in hospital and in the community) and hospital re-admission, was interrogated at least one month following the date of index hospital admission to determine 30-day mortality and 30-day re-admission data. All patients were managed at the discretion of the admitting clinical team according to local CAP guidelines. Ethics approval was granted by the Nottingham Regional Ethics Committee.

Urine samples were collected following admission and transported to the Nottingham University Hospitals Department of Clinical Microbiology, a regional Public Health England (PHE) laboratory. Samples were then placed in frozen storage and transported in batches to the Respiratory and Systemic Infection Laboratory (RSIL) at the Centre for Infections (CfI) at PHE Colindale, London, for pneumococcal serotyping. This was carried out using a multiplex immunoassay (Bio-plex) (Bio-Rad) capable of detecting 14 pneumococcal serotypes (1, 3, 4, 5, 6A/C, 6B, 7F/A, 8, 9V, 14, 18, 19A, 19F and 23F) with 79% sensitivity [18]. Serotype was also determined in bacteraemic adults using slide agglutination using the full set of serotyping latex and factor serum available from Statens Serum Institut Copenhagen. This method is capable of determining all serotypes of pneumococci except the newly described serotype 11E.

PCV7 serotypes were defined by serotypes included in the 7-valent childhood pneumococcal conjugate vaccine (4, 6B, 9V, 14, 18C, 19F, 23F). All other serotypes were deemed non-PCV7 serotypes. Comparisons were made between individuals with PCV7 serotypes versus non-PCV7 serotypes in adults in whom a pneumococcal serotype was determined. A sensitivity analysis was performed by comparing adults with PCV7-serotype CAP versus adults with non-PCV7-serotype CAP and 'untyped' pneumococcal CAP combined. Since PCV13 was introduced to the UK child immunisation schedule in April 2010, a further subgroup analysis was performed following exclusion of adults with CAP due to the extra 6 serotypes included in PCV13 after this period in the study. Those individuals that had both a PCV7 and non-PCV7 serotype were excluded from these analyses.

Statistical analysis was performed using SPSS v 20.0. Pearson's χ^2 test was used to compare categorical variables, and generate odds ratios (OR) and 95% confidence intervals (CI). Continuous variables were compared using Mann–Whitney *U* test. Comparisons were made between adults with PCV7-serotype CAP and non-PCV7-serotype CAP with regard to age, sex, World Health Organisation (WHO) performance status (PS) and the presence of underlying co-morbid illness (malignancy, liver disease, chronic kidney disease (CKD), congestive cardiac failure (CCF), stroke, asthma, chronic obstructive pulmonary disease (COPD), diabetes and dementia; these variables were selected on the basis of pneumococcal serotype specific differences reported in previous studies [15,16,19]. From these variables, independent predictors of PCV7-serotype CAP were established using a multivariate logistical regression model as follows: variables that were associated with PCV7-serotype CAP with a significance level ≤ 0.2 following univariate analysis, were included in the initial step, and remaining variables introduced one at a time into the multivariate model. Variables that were significantly associated with PCV7-serotype CAP ($p < 0.05$) on multivariate analysis or led to a >10% change in the regression coefficient were retained in the final model. A further multivariate model was developed to investigate the independent association between 30-day mortality and PCV7-serotype CAP with adjustment made for potential confounders inclusive of baseline patient demographics, clinical features on hospital admission and disease severity, using the pneumonia severity index (PSI) [20].

3. Results

From a total of 1380 patients identified as having CAP during the study period, 1222 provided consent for the study, 56 of whom were unable to provide a urine sample. Pneumococcal aetiology was identified in 415 of 1166 (35.6%) remaining individuals: the BinaxNOW® pneumococcal urinary antigen test was positive in 239 (57.6%) adults; the Bio-Plex assay was positive in 274 (66.0%) adults; and 40 (9.6%) adults had bacteraemic pneumococcal pneumonia. Of the 287 (69.2%) adults within the pneumococcal cohort in whom a serotype was determined, 13 serotypes were determined using only slide agglutination in bacteraemic samples, and the remainder using the Bio-plex assay. Three individuals had both a PCV7 and non-PCV7 serotype (serotype 4 and 8) and were excluded from subsequent analyses. Median age of the remaining cohort of 284 individuals was 68.2 years (inter-quartile range (IQR) 49.0–79.8), and 153 (53.9%) were male. Thirty-day mortality was 8.5% and median length of stay following exclusion of non-survivors was 6.4 days (IQR 3.8–12.2). Data regarding duration of symptoms prior to admission were available for 450 adults and the median(IQR) was 4 (2–10) days.

PCV7 serotypes were found in 77 (27.1%) individuals and non-PCV7 serotypes in 207 (72.9%); of the adults with non-PCV7 serotypes, 150 (72.5%) had CAP due to one of the 6 additional serotypes included in PCV13. The most prevalent PCV7 serotype was 14 ($n = 45$, 58.4% of PCV7 serotypes) (n=45, 58.4% of PCV7 serotypes) (Fig. 1). Non-PCV7 serotypes with >10 individuals represented included serotype 1 ($n = 45$, 21.7% of non-PCV7 group), 8 ($n = 43$%, 20.8%), 19A ($n = 26$%, 12.6%), 7F/A ($n = 26$%, 12.6%), 5 ($n = 21$%, 10.1%), 3 ($n = 20$%, 9.7%) and 6A/C ($n = 13$%, 6.3%). One patient had 2 PCV7 serotypes (6B + 9V) and another had 2 non-PCV7 serotypes (15A + 18).

3.1. Characteristics of adults with PCV7-serotype CAP

Adults with PCV7-serotype CAP were older (73.3 years versus 65.0 years) and had poorer performance status (WHO PS≥1: 55.8% versus 37.2%) compared to adults with non-PCV7-serotype CAP (Table 1 and Fig. 2). The distribution of individual pneumococcal serotypes by age-group is illustrated in Table 2. The presence of stroke, dementia and CKD as underlying co-morbid illnesses were commoner in adults with a PCV7 serotype. Individuals with stroke