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13-Valent vaccine serotype pneumococcal community acquired pneumonia in adults in high clinical risk groups

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ABSTRACT

There is debate regarding the value of vaccinating adults with the 13-valent pneumococcal conjugate vaccine (PCV-13). This analysis was conducted to investigate the risk of PCV-13 serotype community acquired pneumonia (CAP) in hospitalised adults with co-morbid disease and risk factors for pneumococcal disease in the UK.

Consecutive adults hospitalised (2008–2013) with a primary diagnosis of CAP, were recruited. Pneumococcal aetiology disease was identified by use of pneumococcal urinary antigen detection and serotype identification using a validated multiplex immunoassay or serum latex agglutination. Adults with PCV-13 serotype CAP were compared to those with non-PCV-13 serotype CAP.

Of 2224 patients, PCV-13 serotype CAP was identified in 337 (15.2%) and non-PCV-13 serotype CAP in 250 (11.2%) individuals. Adults aged ≥65 years with one or more clinical risk factors had a significantly lower risk of PCV-13 serotype CAP compared to those aged 16–64 years without clinical risk factors (aOR 0.61, 95%CI 0.41–0.92, p = .018). In a stacked-risk analysis, the presence of incremental clinical risk factors was associated with lower odds of PCV-13 disease (p for trend = .029) Adults with underlying chronic respiratory disease (aOR) 0.56, 95% CI 0.36–0.85, p = .007) and chronic kidney disease (aOR 0.48, 95% CI 0.25–0.92, p = .028) had significantly lower adjusted odds of PCV-13 compared to non-PCV-13 serotype CAP.

This analysis suggests that in the UK, the burden of PCV13 disease is greater in adults outside the traditional 'at-risk' groups compared to adults in 'at-risk' groups.

1. Introduction

Increasing age and the presence of co-morbid diseases are recognised risk factors for pneumococcal disease [1–4]. In addition, pneumococcal attributable mortality is higher in these clinical risk groups [5,6]. Therefore, implementation of appropriate vaccination strategies is important for these individuals. The current UK vaccination policy recommends 23-valent polysaccharide pneumococcal vaccination (PPV-23) in adults at high risk of pneumococcal disease, comprising (a) adults aged between 16 and 64 years with certain co-morbid diseases, and (b) adults aged 65 years and over [7]. However, polysaccharide vaccine effectiveness in these risk groups is debated [8–12]. Immunogenicity studies have shown higher antibody concentrations and functional antibody responses to pneumococcal conjugate compared with polysaccharide vaccination in adults at higher risk of pneumococcal disease including those with human immunodeficiency virus (HIV), chronic obstructive pulmonary disease and older adults [13–15]. Therefore, such patients may benefit from the administration of pneumococcal conjugate vaccination (PCV) in addition to, or in place of the current polysaccharide vaccine. In randomised controlled trials in Malawi and the Netherlands, administration of the pneumococcal conjugate vaccine reduced vaccine-type (VT) invasive pneumococcal disease (IPD) and community acquired pneumonia (CAP) in risk groups of immunocompromised adults with HIV and those over

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the age of 65 years, respectively [16,17]. However, any assessment of the benefits of vaccinating adults with the conjugate vaccine needs to take into account the burden of VT disease in the target group. In the UK, there has been a substantial decrease in adult pneumococcal VT disease as a consequence of herd protection following the introduction of the infant pneumococcal vaccination programme; this decrease is apparent for both invasive and non-invasive pneumococcal disease [18–21]. In patients with IPD, these herd effects appear similar among patients with and without clinical risk factors for pneumococcal disease [3]. There are no such relevant data in adults with non-invasive pneumococcal pneumonia.

In this study, we sought to determine whether hospitalised individuals at high risk of pneumococcal disease are more likely to have PCV-13 serotype CAP compared to non-PCV-13 serotype CAP.

2. Methods

2.1. Study design

We conducted a prospective cohort study of consecutive adult patients admitted, with a primary diagnosis of community acquired pneumonia, to two large university hospitals in Nottingham, between September 2008 and 2013. Combined, these two hospitals cover the catchment area for acute and emergency admissions in the Greater Nottingham area. All patients admitted to medical admissions units were screened every weekday, using radiological and clinical records, to assess for study eligibility. Study eligible patients were aged 16 years or over, presenting with symptoms of a lower respiratory tract infection (at least one of: cough, increasing breathlessness, sputum production and fever), who had radiographic infiltrates consistent with respiratory infection, and who were treated by their clinical team for a diagnosis of CAP. Adults hospitalised in the 10 days preceding the index admission or who had a diagnosis of tuberculosis or post-obstructive pneumonia were excluded. Informed consent was obtained from all study patients; in the event that patients lacked capacity, patient personal consultees were approached for proxy consent. Patient demographics and clinical details were collected from patient records. All study procedures were approved by Nottingham Research Ethics Committee.

2.2. Study population

Routine microbiological investigations were performed at the discretion of the clinical team. In addition, urine samples were taken on admission from each individual for pneumococcal specific microbiological analysis; Binax-NOW® assays were performed for pneumococcal C-polysaccharide urinary antigen detection (UAD) at the local microbiological laboratories whilst the remaining volume of urine was frozen and batch transported to Public Health England (PHE)'s Respiratory and Vaccine Preventable Bacteria Reference Unit in Colindale for serotyping of pneumococcal strains by a multiplex immunoassay (Bio-plex). The Bio-plex assay was validated for detection of pneumococcal serotypes 1, 3, 4, 5, 6A/C, 6B, 7F/A, 8, 9V, 14, 18, 19A, 19F and 23F [22]. The sensitivity and specificity for pneumococcal detection using the Binax-NOW® method, is 74% and 97%, respectively and for the Bio-plex method, is 79% and 99%, respectively [22,23]. Bacteraemic cases of CAP due to *Streptococcus pneumoniae* were identified and serotyped by serum latex agglutination at PHE's reference laboratory. Patients were considered to have pneumococcal CAP if any of the following criteria were met: (a) a positive pneumococcal UAD, or (b) a positive blood culture for *S pneumoniae,* or (c) pneumococcal serotype detection by the Bio-plex assay.

2.3. Statistical considerations

Statistical analyses were performed using Stata/IC 13.1 (©StataCorp., 2013). Serotypes were grouped into PCV-7 types (serotypes 4, 6B, 9V, 14, 18C, 19F and 23F), 'additional' PCV-13 types not present in PCV-7 (serotypes 1, 3, 5, 6A/C, 7F/A, 19A) and 'other' non-PCV-13 serotypes. PCV-13 disease was defined as the identification of one or more of serotypes in either the PCV-7 or 'additional' PCV-13 groups. Non-PCV-13 disease was defined as the isolation of any other pneumococcal serotype or the presence of 'untyped' non-invasive pneumococcal CAP (based on a positive UAD). Baseline characteristics and putative co-morbid disease risk factors for PCV-13 disease were compared using Pearson's chi-square or Fisher's tests for categorical variables, and the Mann Whitney *U* test for non-parametric continuous variables. The independent association between baseline co-morbidity and PCV-13 disease compared to non-PCV-13 disease was examined using a multivariable logistical regression model; those co-morbid diseases with a p value of <0.2 on univariate analysis were included in the multivariable model. Likelihood ratio tests were used to determine the best model fit for continuous variables. Secondary analysis were conducted examining the odds of PCV-13 disease in (a) all 'at-risk' individuals (defined as those aged 16–64 with a clinical risk factor for pneumococcal disease *or* those ≥65 years), (b) individuals stratified according to age (dichotomised at 65 years) and the presence of a clinical risk factor for pneumococcal disease: (1) aged 16–64 years without a clinical risk factor, (2) aged 16–64 years with one or more clinical risk factors, (3) aged ≥65 years without a clinical risk factor, (4) aged ≥65 years with one or more clinical risk factors and (c) individuals with increasing numbers of clinical risk factors; gender was included *a priori* in these models. Clinical risk factors for pneumococcal disease were defined as those eligible for pneumococcal vaccination in the UK as described in PHE's 'Immunisation against Infectious Diseases'; in brief, risk factors included chronic respiratory disease, chronic heart disease, chronic kidney disease, chronic liver disease, immunosuppression, diabetes, splenic dysfunction and individuals with cerebrospinal fluid (CSF) leaks or cochlear implants [7]. Immunosuppression was defined as the presence of splenic dysfunction, haematological disease including malignancy, solid organ or bone marrow transplant, immunodeficiency, treatment with immunosuppressive medication (not including steroids) or HIV; all other case definitions were derived from a previous study examining clinical risk groups in pneumococcal disease [24].

Incidence data for pneumococcal CAP in the Greater Nottingham area were calculated using data on population demographics collected from (a) the National Infection Service, PHE, for adults aged 16–64 with clinical risk factors, and (b) the UK census (2011) for adults aged ≥65 years [25]. As there is no national registry of risk groups for pneumococcal disease, population demographic data for influenza risk groups were taken as a surrogate measure for incidence calculations [26].

3. Results

3.1. Study population

Over the 5 year study period, 2702 patients were eligible for study inclusion. Of these, 284 (10.5%) were subsequently found to have an alternative diagnosis to CAP and in a further 194 patients, study consent was not obtained. The final study cohort consisted of 2224 adults. Patients in whom consent was not obtained were older (median age: 82 years, IQR 73–89 years versus 71 years, IQR 56–80 years, $p < .001$) and were more likely to have chronic kidney disease (13.4% versus 7.6%, $p = .004$), cerebrovascular

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