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The epidemiology of community acquired bacteremic pneumonia, due to *Streptococcus pneumoniae*, in the Top End of the Northern Territory, Australia—Over 22 years

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ABSTRACT

Background: Diseases caused by *Streptococcus pneumoniae* continue to cause substantial morbidity and mortality throughout the world. Furthermore, detrimental outcomes are more pronounced in some populations—such as those living in third world poverty, and Indigenous people who live in developed nations.
Methods: This study describes the epidemiology of blood culture positive *S. pneumoniae* community-acquired pneumonia (CAP) in the Top End of the Northern Territory of Australia. Demographics, indigenous status, medical risk factors, serotype and outcomes were collected from adults presenting to hospital with blood culture positive *S. pneumoniae* CAP, from 1987 to 2008.
Results: We report 205 cases, with a median age of 40 years. The average overall incidence rate ratio was 10.3 for indigenous adults compared with non-indigenous adults. There was no statistical difference between incidence rates pre and post-23-valent pneumococcal polysaccharide vaccine (23vPPV) introduction. Serotypes in presenting cases were predominantly (84.7%) 23vPPV types. The whole-population logistic regression model identified significant adjusted relative risks: 95% CI, for age 45 and older 1.6: 1.1, 2.2, indigenous 5.9: 3.7, 9.5, diabetes 2.3: 1.6, 3.3, excess alcohol 4.8: 2.8, 8.3, smoking 2.7: 1.9, 3.7 with indigenous + excess alcohol 18.5: 17.3, 19.7 as predictive for bacteremic *S. pneumoniae* CAP presentation.
Conclusions: Our results suggest that, the national 23vPPV program appears to be under-utilized. An integrated Public Health approach vigorously targeting indigenous adolescents, before substances such as alcohol and smoking are habitual, together with increased vaccine coverage, will reduce the burden of pneumococcal disease in this population.

1. Introduction

Streptococcus pneumoniae continues to be the leading causative agent for community-acquired pneumonia (CAP) in adults internationally [1–3]. Despite the breakthrough discovery of penicillin in 1928 and significant improvements in medical management of pneumonia, deaths continue to occur from *S. pneumoniae* CAP, especially for indigenous persons often at alarming rates [4–7]. In Australia during the 1990s, respiratory disease was the leading cause of hospitalizations for Indigenous men, and the second highest for Indigenous women [8]. More recently, Indigenous adults continue to be hospitalized for respiratory diseases at four times the rate of non-Indigenous adults [9], with higher rates of non-vaccine serotype invasive pneumococcal disease (IPD) reported in Indigenous people [10–12], especially in the Northern Territory (NT). Furthermore, drug resistance to *S. pneumoniae* is worrisome, with the highest rate of intermediate penicillin susceptibility (34%) in Australia, reported from NT's capital city, Darwin [13].

The NT has the highest percentage of Indigenous residents (30%) in Australia, which compares with 2.5% nationwide [14]. Indigenous persons have higher rates of poor health and health risks, such as smoking; rates in remote-living Indigenous persons are higher still [15] Annual IPD rates in the NT are up to five times higher than the national average [12]. In 2009, the IPD rate for the NT was 40.5/100,000 population, compared with 7.2/100,000

Abbreviations: CXR, chest X-ray; CLD, chronic lung disease; CRD, chronic renal disease; CAP, community-acquired pneumonia; CI, confidence interval; GLM, generalized linear model; IR, incidence rates; ICU, intensive care unit; IPD, invasive pneumococcal disease; NT, Northern Territory; RR, relative risk; RDH, Royal Darwin Hospital; 7PCV, 7-valent pneumococcal conjugate vaccine; 23vPPV, 23-valent pneumococcal polysaccharide vaccine.

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population for Australia [12]. Furthermore, the ill health experienced by remote Indigenous residents overlies complex historical social struggles, creating even greater challenges for Public Health initiated disease prevention and reduction.

Vaccination appears to be a straightforward solution to reducing the burden of pneumococcal disease by; however, in practice it has proved an evasive target. The current national 23vPPV schedule includes: all Indigenous adults ≥15 years regardless of risk factors, with revaccination every 5 years to a maximum of three doses [16,17]. For non-Indigenous Australians, the current recommendation is for persons aged ≥65 years, or ≥10 years with an underlying predisposing risk [17]. In the NT, serotypes contained in the 23-valent-pneumococcal polysaccharide vaccine (23vPPV) account for 85% of disease in non-Indigenous and 68% in Indigenous persons over 2 years of age [18]. However, there has been little evidence of a reduction of IPD in NT Indigenous adults [11,16,18,19] since 23vPPV introduction in 1995. A recently published Cochrane review reports strong evidence for 23vPPV efficacy and effectiveness against bacteremic pneumococcal disease in adults [20]. Estimates of vaccine efficacy for invasive disease were 74% from randomized studies and 52% from observational studies; however, the meta-analysis failed to demonstrate vaccine efficacy in adults with chronic illness [20].

This study aims to establish the epidemiology of blood culture positive *S. pneumoniae* CAP over 22 years (1987–2008) of admissions to adult wards at Royal Darwin Hospital (RDH) the referring hospital for the NT. We aim to identify differences in presentation characteristics, serotypes and outcomes throughout the study period.

2. Materials and methods

This study was performed in Darwin, the largest urban city in the NT, located in the tropical north (12°S, 130°E). The "Darwin health division" defines the urban and rural area confined to the coastal north west of the NT that refers patients to RDH the 300 bed teaching hospital. Darwin urban plus Darwin rural health region covers an area of 167,803 km^2, with a population of 114,537 [21]. We examined all adult cases of primary diagnosis blood culture positive *S. pneumoniae* CAP, who presented to RDH, between 1987 and 2008. The study design was comprised of two cohorts; a prospective cohort study 1987–1998, (cohort 1); in which all clinical data was collected upon notification by the infection control unit. While data from Cohort 2, 1999–2008, were retrospectively collected via medical record review. CAP was defined as a pulmonary infiltrate on chest X-ray (CXR) with symptoms consistent with pneumonia; or diagnosed upon autopsy. Pneumococcal pneumonias based on microbiology from sites other than blood were excluded. To avoid the inclusion of possible nosocomial infections, episodes of hospitalization within 6 weeks of pneumococcal admission were excluded. Information on smoking status and alcohol consumption could not be located on one case; analysis on these risks excess excludes that case.

A standardized data collection form was used to collect: demographic characteristics, presenting risk factors, pneumococcal serotype (where available) and outcomes. We defined; hazardous alcohol intake as an average daily consumption greater than six standard drinks (60 g alcohol) for males and four (40 g alcohol) for females; chronic lung disease (CLD) as a documented diagnosis of chronic obstructive airways disease; chronic renal disease (CRD) as a creatinine of >150 μmol/L prior to this admission; cardiac disease as a history of rheumatic heart fever, congestive cardiac failure, cardiomyopathy or ischaemic heart disease. The "dry season" was defined from May to November inclusive and serotyping was performed using standardized techniques as previously reported [16].

3. Statistical analysis

Student's *t*-tests were performed on "age" (square root transformed) for males versus females and Indigenous versus non-Indigenous [22]. Analysis of risk factors was performed as previously reported [23–26]. We present the risk factors from both cohorts combined. Serotypes were compared after stratification by years according to vaccination serotype, for 23vPPVand 7-valent pneumococcal conjugate vaccine (7PCV), untype-able serotypes were excluded.

For calculating incidence rates (IR) and whole-population predictors for acquiring *S. pneumoniae* CAP, Darwin's urban and rural statistical region population (stratified by age, sex, and ethnicity) were provided by Northern Territory Government [27] as previously described [28]. The standard year was chosen as 1998 to reflect the mean population as the midpoint in the study period [28]. Incidence rates were calculated as cases/denominator/years/100,000 with confidence intervals calculated assuming a Poisson distribution. A binomial generalized linear model (GLM), with logit link compared the number of annual cases by Indigenous status, weighted by population. As the binomial response assumes a logit link the equation used is the simple logistic regression in the form of:

$$\mathrm{Log}_e\left[\frac{P}{1-P}\right] = \alpha + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_n x_n \quad (1)$$

where P is the probability of a case, x_1 are medical risk factors, and $\alpha, \beta_1, \ldots, n$ are constants estimated from the data.

Rates and population denominators for hazardous alcohol consumption [9,29], diabetes [29,30], smoking [31] were required to create the covariate matrix. Using published population estimates and rates of disease or behavioral risk, the subsequent extrapolated estimates were calculated [28]. We applied the same rates of hazardous drinking to diabetics and non-diabetics alike, assuming that the proportion of high risk drinking among diabetics and the same for non-diabetics, as the general population [32]. A multivariate logistic regression model (1) was applied to the covariate matrix. The final model for analysis included the following predictors; age (15–45, ≥45), gender (M/F), ethnicity (Indigenous/non-Indigenous), diabetes, hazardous alcohol consumption and current smoking. Odds ratios were used as an estimator of relative risk (RR) for this cohort study, calculated with 95% confidence intervals (CI) [33]. All analyses were performed using Intercooled STATA version 11.0 (Stata Corporation, Texas). The Joint Institutional Ethics Committee of the Royal Darwin Hospital and Menzies School of Health Research provided ethical approval.

4. Results

A total of 205 cases of bacteremic, radiologically confirmed CAP due to *S. pneumonia* presented in 197 persons during the study period. Indigenous patients were significantly younger in age on presentation than non-Indigenous (*t*-test, $P < 0.0001$) (Table 1). Of the available serotypes ($n = 148$), 16.22% were un-type able, and were excluded from analysis. Type-able isolates were predominantly 23vPPV serotypes 105/124 (84.7%) (Fig. 1). There was no significant decrease in presentations with 23vPPV or 7PCV serotypes (serotype data only available since 1994), since vaccination 1995, and 2001 respectively (Table 2).

Of the combined presentations, 64% were aged less than 45 years (Table 3). Males and Indigenous patients were both overrepresented with 61% and 67% of the total admissions, respectively. Similarly, 62% of presentations consumed alcohol at hazardous levels. The minority of patients presented with no risk factors 5% ($n = 11$), and the majority (69%) presented during dry season