

PNEUMOCOCCAL SEROTYPE DISTRIBUTION IN ADULTS HOSPITALIZED WITH RADIOLOGICALLY CONFIRMED COMMUNITY-ACQUIRED PNEUMONIA IN MALMÖ, SWEDEN



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Background

Background Skåne is the third largest region in Sweden and introduced PCV7 in its' pediatric vaccination schedule in Jan 2009, followed by PCV10 in May 2010, PCV13 in May 2014, and PCV10 again from May 2018. Both PCV13 and PCV10 are administered in a 2+1 schedule and Sweden's pediatric PCV program has led to substantial declines in invasive pneumococcal disease as well as in non-invasive disease amongst children.^{1,2} An incidence of CAP hospitalization in Sweden between 2060 – 2140 per 100,00 population per year has been estimated and Streptococcus pneumonice has been diagnosed in 30% to 38% of hospitalized community acquired pneumonia (CAP) cases. However, these studies were carried out before the introduction of PCV1s in pediatric and adult populations in Sweden.³⁶ Currently, two pneumococcal vacines are licensed for use in adults: a 13-valent pneumococcal conjugate vaccine (PCV13, containing serotypes 1, 4, 4, 5, 68, 6A, 7F, 9V, 14, 18C, 19A, 197, 23F) and a 23-valent pneumococcal polyscachanide vaccine (PPV23, containing serotypes 1, 3, 4, 5, 68, 7F, 9V, 14, 18C, 19A, 197, 23F, and 24-valent pneumococcal colors and therain the original UAD1 assay distents. There urinary antigen detection (UAD) assay is a robust tool for clinical and epidemiological evaluation of both invasive and non-invasive pneumococcal disease in adults 20F and 33F, and a 20-valent PCV to include PCV15 serotypes 8, 10A, 11A, 12F and 156. "The PTiffer urinary antigen detection (UAD) assay is a robust tool for clinical and epidemiological evaluation of both invasive and non-invasive pneumococcal disease in adults 20F and 33F, and a 20-valent PCV to include PCV15 serotyping methods from culture. The original UAD1 assay detects Streptococcus pneumonice (Spn) serotypes scovered by PCV13. In addition, the UAD2 assay has been developed to detect 11 additional serotypes covered by PCV13. In addition, the UAD2 assay has been developed to detect 11 additional serotypes are adverted by the provides score days PCV10. In additind the end ta

lack of a suitable gold standard. In Sweden the serotype distribution of IPD amongst adults has previously been described', but serotype distribution in non-bacteremic CAP is unknown. In the Community Acquired Pneumonia Immunization Trial in Adults (CAPITA) PCV13 demonstrated efficacy in preventing both bacteremic and non-bacteremic vaccine-type (VT) CAP as well as VT-IPD in older adults.⁹

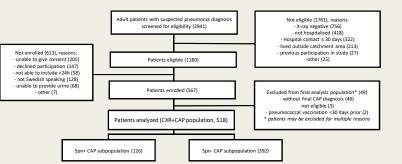
Methods

This was a prospective, observational study of adults >18 years of age, hospitalized with CAP. Study participants were recruited between September 2016 to September 2018 at the Skåne University Hospital (SUS). SUS in Malmö is a tertiary referral hospital with 600 beds serving a population of 400,000 persons. The primary objective of the current study was to estimate the proportion of pneumococcal conjugate vaccine type Streptococcus pneumoniae (Spn) serotypes detected by either the UAD assay or bacterial culture among adults 218 years of age presenting with clinically and radiographically confirmed CAP. Patients with an admission diagnosis of pneumonia or a pneumonia-related diagnosis were evaluated for study eligibility. To be eligible, participants had to: (1) be aged 18 years and older; (2) present with a clinically suspected CAP with the presence of two or more of the following signs or symptoms: fever or hypothermia within 24 hours of enrollment, chills or rigors, pleuritic chest pain, cough, sputum production, dyspnea, tachypnea, malaise, abnormal auscultatory findings suggestive of pneumonia; (3) have a radiographic finding that was consistent with pneumonia; (4) be able and willing to provide urine sample(s); (5) have signed and dated an informed consent form; (6) be a resident of the catchment area (Malmö, Vellinge and Svedala). Exclusion criteria included: (1) subjects already hospitalized for >48 hours; (2) Hospital acquired pneumonia (e.g. develop signs and symptoms of pneumonia after being hospitalized for 48 hours or more) during the previous 30 days; (3) subjects who were tional site staff members directly involved in the conduct of the trial and their family members, or site staff members otherwise supervised by the investigator; (4) previous enrollment in the study within the previous 30 days; (5) subject inappropriate for entry into the study by judgment of the investigator. If eligible for enrollment, subject demographic, immunization (pneumococcal and influenza vaccines within the past year) and medical history information were collected. Culture results from normally-sterile sites (blood, pleural fluid) and respiratory secretions (sputum, tracheal aspirate, bronchial washings) were collected as a part of the subject's standard medical care and recorded in case-report form. For subjects not having blood cultures collected as standard medical care, the respective specimen was collected as a study procedure. Streptococcus pneumoniae (Spn) positive blood culture isolates were serotyped by a multiprime PCR and Quellung reaction. Urine was tested by the pan-pneumococcal urinary antigen test (BinaxNOW*) and Pfizer's proprietary serotype-specific urine antigen detection assays (UAD1/UAD2). Patients were followed up 3 months after hospital discharge when also vital status was assessed (alive or deceased). The study was approved by The Regional Ethical Review Board in Lund, Skåne, on 25 April 2016.

Results

Of 567 enrollees, 518 had chest x-ray positive (CXR+) CAP. Spn serotypes were identified by UAD or culture isolates (Figure 1 and 2).

Figure 1. Patient screening, eligibility, enrollment and analysis population (n):



The mean age of enrolled subjects was 69.0 years. 42.7% of subjects v ith CAP had at least one at-risk condition and 34.7% were considered high risk. (Table 1). Most common comorbidities reported in 18-64 years were chronic pulmonary disease (COPD) 34/168 comorbidities reported in 18-64 years were chronic pulmonary disease (COPD) 34/168 (20-2%), diabetes 20/169 (13:8%), malignaroy including leukemia/hymphoma 17/168 (10.1%), rheumatology/connective tissue disease 11/169 (6.5%), myocardial infarction 9/169 (5.3%), Most common comorbidities reported in 265 years were COPD 132/349 (37.8%), congestive heart failure 9/169 (2.3%), Most common comorbidities (4.9%), malignaroy including leukemia/hymphoma 33/348 (2.3%), Myocardial infarction 77/349 (22.1%), diabetes 65/349 (13.6%) and renal disease 38/349 (10.0%), 11.5% of subjects reported they had previously received any pneumococcal vaccine (Table 1).

Table 1. Baseline Characteristics, Risk factors and Medical History

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Age	18-64 years, n=169 (32.6%)	≥65 years, n=349 (67.4%)	≥18 years, n=518 (100%)			
Mean (SD)	48.3 (12.89)	79.1 (7.99)	69.0 (17.48)			
Median	52.0	79.0	73.0			
Min, Max	18, 64	65, 99	18, 99			
Sex						
Male	92 (54.4%)	190 (54.4%)	282 (54.4%)			
Female	77 (45.6%)	159 (45.6%)	236 (45.6%)			
Prior Vaccination						
Influenza vaccine	13/165 (7.9%)	159/329 (48.3%)	172/494 (34.8%)			
Any pneumococcal vaccine	5/165 (3.0%)	51/324 (15.7%)	56/489 (11.5%)			
Lifestyle risk factors						
Smoker	46/119 (38.7%)	51/164 (31.1%)	97/283 (34.3%)			
Current alcohol abuse	10/168 (6.0%)	8/342 (2.3%)	18/510 (3.5%)			
Current illicit drug use	5/169 (3.0%)	1/347 (0.3%)	6/516 (1.2%)			
Risk level						
High risk*	39/169 (23.1%)	141/349 (40.4%)	180/518 (34.7%)			
At risk ^b	52/169 (30.8%)	169/349 (48.4%)	221/518 (42.7%)			
Low risk	78/169 (46.2%)	39/349 (11.2%)	117/518 (22.6%)			

disease. Is At risk: choic obstructive pulmonary disease (COPO), asthma, congestive heart failure (CHF), coronary artery disease (CAD), diab sectors-obased white anti-immune disorders and treatment with proton pump inhibitors.

ent Medical Condition. Health Care Resource Utilization and Mortality

Table 2. Patient Medical Condition, Health Care Resource Offiziation and Mortality					
Pneumonia Severity Index (PSI)	18-64 years, n=169 (32.6%)	≥65 years, n=349 (67.4%)	≥18 years, n=518 (100%)		
Mean (SD)	63.6 (28.1)	106.6 (30.5)	92.6 (35.9)		
PSI Grade (n (%))					
GRADE I	60 (35.5%)	0 (0.0%)	60 (11.6%)		
GRADE II	49 (29.0%)	41 (11.7%)	90 (17.4%)		
GRADE III	30 (17.8%)	76 (21.8%)	106 (20.5%)		
GRADE IV	27 (16.0%)	168 (48.1%)	195 (37.6%)		
GRADE V	3 (1.8%)	64 (18.3%)	67 (12.9%)		
CRB-65 score, mean (SD)	0.2 (0.5)	1.3 (0.5)	0.9 (0.7)		
Hospitalization Duration, mean (SD) ^a	5.7 (4.3)	10.0 (22.6)	8.6 (18.7)		
Mortality	4 (2.4%)	41 (11.7%)	45 (8.7%)		
Death within 30 days from hospital admission	2 (1.2%)	19 (5.4%)	21 (4.1%)		
Death within 90 days from hospital admission	3 (1.8%)	40 (11.5%)	43 (8.3%)		
Death in hospital	1 (0.6%)	18 (5.2%)	19 (3.7%)		

Mean pneumonia severity index (PSI) score was 92.6 and 106.6 in ≥18 and ≥65 years old groups respectively. Mean CRB-65 score was 0.9 and 1.3 in ≥18 and ≥65 years of age respectively. (Table 2).

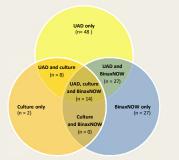
For subjects ≥ 18 years, mean hospital stay was 8.6 days (±6.0) and mortality within 30 days from hospital admission was 4.1% (Table 2).

In study participants with CXR+CAP aged ≥18 years. Spn+ was detected by any test (BinaxNOW, UAD or culture) in 126/518 (24.3%) subjects (Figure 1 and 2).

Table 3. Vaccine serotypes and categories detected by UAD or blood culture, and Spn+ detected from any diagnostic method (UAD, Bina NOW[®] or culture).

Pneumococcal Conjugate Vaccines (PCVs)	18-64 years, n=169 (32.6%)	≥65 years, n=349 (67.4%)	≥18 years, n=518 (100%)		
PCV13 serotypes	21 (12.4%)	35 (10.0%)	56 (10.8%)		
4	0 (0.0%)	3 (0.9%)	3 (0.6%)		
14	0 (0.0%)	2 (0.6%)	2 (0.4%)		
18C	1 (0.6%)	1 (0.3%)	2 (0.4%)		
19F	0 (0.0%)	1 (0.3%)	1 (0.2%)		
23F	1 (0.6%)	0 (0.0%)	1 (0.2%)		
3	9 (5.3%)	17 (4.9%)	26 (5.0%)		
5	3 (1.8%)	5 (1.4%)	8 (1.5%)		
6A	0 (0.0%)	3 (0.9%)	3 (0.6%)		
7F	2 (1.2%)	0 (0.0%)	2 (0.4%)		
19A	6 (3.6%)	4 (1.1%)	10 (1.9%)		
PCV15 serotypes	23 (13.6%)	42 (12.0%)	65 (12.5%)		
PCV15 serotypes not in PCV13	2 (1.2%)	7 (2.0%)	9 (1.7%)		
22F	0 (0.0%)	6 (1.7%)	6 (1.2%)		
33F	2 (1.2%)	1 (0.3%)	3 (0.6%)		
PCV20 serotypes	35 (20.7%)	53 (15.2%)	88 (17.0%)		
PCV20 serotypes not in PCV15	13 (7.7%)	11 (3.2%)	24 (4.6%)		
8	7 (4.1%)	3 (0.9%)	10 (1.9%)		
10A	0 (0.0%)	1 (0.3%)	1 (0.2%)		
11A	4 (2.4%)	6 (1.7%)	10 (1.9%)		
12F	0 (0.0%)	1 (0.3%)	1 (0.2%)		
15B	2 (1.2%)	0 (0.0%)	2 (0.4%)		
Non-PCV20 serotypes	5 (3.0%)	9 (2.6%)	14 (2.7%)		
9N	3 (1.8%)	4 (1.1%)	7 (1.4%)		
17F	1 (0.6%)	3 (0.9%)	4 (0.8%)		
12*	0 (0.0%)	1 (0.3%)	1 (0.2%)		
35B*	0 (0.0%)	1 (0.3%)	1 (0.2%)		
37*	1 (0.6%)	0 (0.0%)	1 (0.2%)		
Spn+ from any diagnostic method*	46/169 (27.2%)	80/349 (22.9%)	126/518 (24.3%)		
*UAD, BinaxNOW or culture (sterile and non-sterile)					

Figure 2. Distribution of Spn detection by diagnostic method among all study participants with Spn+ CXR+CAP (n = 126). The UAD1/2 test and BinaxNOW® was performed for all enrolled patients (567). In 522 patients, any cultured for Spn was performed (culture from a normally-sterile site in 519 patients with and culture rom respiratory secretions in 52 patients).



The most common serotypes identified were serotypes 3, 19A, 8, 11A, 5 and 22F. PCV13 serotypes were found in 56/518 (10.8%) of CXR+CAP cases. PCV20 serotypes were found in 88/518 (17.0%) of CXR+CAP cases (Table 3). The UAD1/2 test also detects the non-PCV20 serotypes 9N, 17F, 2 and 20 and some of these serotypes were found in small proportions in the study population. All remaining serotypes were only detected by bacterial culture (Table 3). In subjects 18-<65 years of age among those with high-risk, at-risk, and not at-risk conditions, PCV20-type CAP as found in 10/39 (25.6%), 13/52 (25.0%), and 12/78 (15.4%) of CAP cases, respectively. A similar trend was also observed in ≥65 years old subjects (Table 4).

Table 4. Vaccine coverage per age group and risk level

	PCV13 serotypes, n (%)	PCV15 serotypes, n (%)	PCV20 serotypes, n (%)			
18-<65 years of age (n=169)						
High risk (n=39)	9 (23.1%)	9 (23.1%)	10 (25.6%)			
At-risk (n=52)	5 (9.6%)	6 (11.5%)	13 (25.0%)			
Low risk (n=78)	7 (9.0%)	8 (10.3%)	12 (15.4%)			
≥65 years of age (n=349)						
High risk (n=141)	16 (11.3%)	18 (12.8%)	24 (17.0%)			
At-risk (n=169)	15 (8.9%)	19 (11.2%)	24 (14.2%)			
Low risk (n=39)	4 (10.3%)	5 (12.8%)	5 (12.8%)			
All ≥18 years of age (n=518)						
High risk (n=180)	25 (13.9%)	27 (15.0%)	34 (18.9%)			
At-risk (n=221)	20 (9.0%)	25 (11.3%)	37 (16.7%)			
Low risk (n=117)	11 (9.4%)	13 (11.1%)	17 (14.5%)			

Conclusions

Despite Sweden's robust pediatric PCV immunization program, a persistent burden of adult CAP was caused by PCV13 pneumococcal serotypes. These findings emphasize the limits of indirect effects from pediatric immunization for protection of the elderly and younger adults with high-risk and at-risk conditions, and support direct vaccination programs for these target groups. The proportion of CAP caused by PCV20-types was highest in patients with underlying at-risk and high-risk conditions, pointing to a possible association between these serotypes and underlying risk factors.

Serotype 3 contributed to 20-21% of all Spn+ CXR+CAP, depending on age group. In this regard it should be noted that in the CAPITA-trial PCV13 the efficacy against serotype 3 CAP was consistent with the vaccine's overall efficacy.¹⁰

Compared to PCV13 and PCV15, the additional serotypes included only in PCV20 lead to a substantial increase in the coverage of pneumococcal CAP in Swedish adults. To ccurately account for the potential impact of adult pneumococcal vaccination however, not only serotype coverage, but also expected vaccine effectiveness against non-bacteremic CAP, duration of protection, and expected cross-protectior against vaccine-related serotypes needs to be considered.

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