


RESEARCH PAPER



Distribution of 13-Valent pneumococcal conjugate vaccine serotype *streptococcus pneumoniae* in adults 50 Years and Older presenting with community-acquired pneumonia in Israel

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ABSTRACT

Background: Community acquired pneumonia (CAP) is a major cause of morbidity and mortality worldwide, and is a leading cause of hospitalization in previously healthy individuals without predisposing risk factors or comorbidities. In this study we determined PCV13 serotype distribution in adults aged ≥ 50 years with radiographically confirmed CAP in Israel.

Methods: Subjects aged ≥ 50 years were enrolled from one of three hospitals (Emek Medical Center, Meir Medical Center and Sheba Medical Center) from March 2014 to July 2015. Information was collected on subject demographics, comorbidities, risk factors, and pneumococcal vaccine immunization status. Subjects presented with suspected CAP supported by radiographic evidence, and provided a urine sample and informed consent. Subjects without radiographic confirmation of CAP or who received PPSV23 within 30 days of study enrollment were excluded from the final analysis. Serotype distribution was performed using the urinary antigen detection (UAD) assay and/or microbiological culture.

Results: Overall, 498 subjects with radiographically confirmed CAP were enrolled in the study. Eighty subjects (16.1%) were positive for any *S. pneumoniae* serotype by ≥ 1 assay, and 38 (7.6%) were positive for PCV13 serotypes via the UAD. The overall 30-day mortality rate was 1.2%, though *S. pneumoniae* was not isolated from any case leading to death.

Conclusion: Despite six years of high pneumococcal immunization coverage in children in Israel, we have shown that 7.6% of CAP cases among adults in Israel remain related to PCV13 serotypes; and that the burden of PCV13 may be as high as 47% of observed pneumococcal CAP.

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Introduction

Community acquired pneumonia (CAP) is a major cause of morbidity and mortality worldwide,^{1–4} and is a leading cause of hospitalization in previously healthy individuals without predisposing risk factors or comorbidities.⁵ CAP can be caused by a variety of agents; however *Streptococcus pneumoniae* is the most commonly diagnosed pathogen.⁶ Accordingly, an early study of CAP etiology in Israel showed that 42% of CAP cases among adults admitted to hospitals were due to *S. pneumoniae*.⁷

In an effort to reduce the impact of pneumococcal disease, the 7-valent pneumococcal conjugate vaccine (PCV7) was first licensed in Israel in 2007.⁸ The vaccine was then introduced into the Israeli National Immunization Plan (NIP) in 2009, to be administered at 2, 4 and 12 months of age, with a catch-up campaign in all children < 2 years old.⁸ Subsequently, in late 2010 the 13-valent pneumococcal conjugate vaccine (PCV13) replaced PCV7 in the Israeli NIP, without further catch-up.⁸ As

of June 2013, the proportion of 7–11 month old children who had received ≥ 2 doses of any PCV13 was 89%.⁹ The PCV13 vaccine was approved for use in adults with high-risk conditions in Israel in 2013, but was not provided until 2016.¹⁰ Current PCV vaccine coverage among adults in Israel is still low, while PPSV23 vaccine is recommended for adults ≥ 65 years old.

The use of PCV7/13 vaccines has resulted in a significant decline in the overall occurrence of both invasive and non-invasive pneumococcal disease in Israel. Decreases in vaccine-type invasive pneumococcal disease (IPD) have been seen amongst both children and adults.^{10,11} Vaccination with PCV7/13 has also had an impact on the occurrence of CAP in Israel. Greenberg et al. reported a decrease in annual CAP incidences (per 1,000 inhabitants) in children < 5 years old from a mean of 13.8 ± 0.9 in the pre-PCV period to 11.2 ± 2.7 in the PCV7 period and 7.4 in the PCV13 period, representing reductions of 13% and 47%, respectively.⁹ Less is currently known about the

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current incidence and serotype distribution of pneumococcal serotypes in adults with CAP in Israel.

Understanding the distribution of pneumococcal serotypes present in CAP is important for optimizing pneumococcal disease control in Israel and around the globe. In the past, the lack of a reliable and specific diagnostic assay greatly limited epidemiologic measurement of non-invasive pneumococcal diseases such as CAP. However, the recent development of a serotype specific UAD multiplex assay that allows for the identification of 13 pneumococcal serotypes (serotypes 1, 3, 4, 5, 6A/C, 6B, 7F/A, 9V/A, 14, 18 [A, B, C, F], 19A, 19F, and 23F) in the urine of subjects with CAP allows for a more thorough investigation of serotype distribution. Using this UAD assay we have investigated the proportion of radiographically-confirmed pneumonia caused by pneumococcal serotypes included in the 13-valent pneumococcal conjugate vaccine (PCV13) in adults 50 years and older at three sites in Israel.

Materials and methods

Objective

The study objective was to determine PCV13 serotype distribution in adults aged ≥ 50 years with radiographically confirmed CAP presenting to 3 hospitals in Israel using the UAD assay and/or microbiological culture.

Design and subjects

This study was approved by institutional review boards and/or independent ethics committees of Emek Medical Center (IRB#0141-13-EMC), Meir Medical Center (IRB#0261-13 MMC) and the Sheba Medical Center (IRB#0789-13). The study was conducted in compliance with the amended Declaration of Helsinki, the International Conference on Harmonisation, Good Clinical Practice Guidelines, and all local regulatory requirements. Written informed consent was obtained from all subjects before enrollment and performance of any study-related procedures.

Subjects aged ≥ 50 years were enrolled from one of three hospitals: Emek Medical Center, in Afula, Northern Israel, with 550 beds, Meir Medical Center, in Kfar Saba, Hasharon District, with 740 beds and Sheba Medical Center, the largest tertiary hospital in Israel, in Ramat-Gan, Central Israel, with 1400 Acute care beds, from March 2014 to July 2015. Information was collected on subject demographics, comorbidities, risk factors, and pneumococcal vaccine immunization status. Subjects were ≥ 50 years of age, presented to one of the three hospitals with suspected CAP supported by radiographic evidence (some cases were later designated as healthcare-associated pneumonia ([HCAP]), and provided a urine sample and informed consent. Subjects without radiographic confirmation of CAP or who received PPSV23 within 30 days of study enrollment were excluded from the final analysis.

Streptococcus pneumoniae detection

Each subject underwent three assessments for the detection of *S. pneumoniae* CAP: 1) microbiology cultures collected per

standard of care (blood, pleural fluid, bronchiolar lavage, tracheal aspirate, and respiratory cultures); overall low sensitivity / high specificity¹²; 2) BinaxNOW[®] assay (Alere North America, Orlando, FL, USA) for overall detection of *S. pneumoniae* in the urine (52% to 86% sensitivity, 83% to 97% specificity compared to blood culture¹³⁻¹⁷) and 3) the proprietary 13-valent multiplex UAD assay (Pfizer Research, Pearl River, NY, USA) for specific detection of 13 *S. pneumoniae* serotypes in the urine (97% sensitivity and 100% specificity compared to blood culture).¹⁷ UAD results were not used diagnostically. All analyses were descriptive.

Results

Overall, 498 subjects with radiographically confirmed CAP were enrolled in the study (Table 1). The mean age of enrollees was 72.6 (median 73, range 50–101), and half of all subjects had previously received PPSV23. The most common at-risk conditions were diabetes mellitus (40.8%), coronary artery disease (33.3%) and chronic obstructive pulmonary disorder (32.1%) (Table 1). Most patients received antibiotic treatment (78.9%) before recruitment and 9.6% received prior immunosuppressive therapy. Six deaths were reported; 5 were due to pneumonia with no isolation of *S. pneumoniae*, and 1 was reported as not directly attributed to the infection. The overall mortality rate measured 30 days after enrollment was 1.2%.

Among the 498 subjects with radiographically confirmed CAP, 80 (16.1%) were positive for any *S. pneumoniae* serotype by ≥ 1 assay (Fig. 1/Table 2). In total, 38 subjects (7.6%), 48 subjects (9.6%) and 17 subjects (3.7%) were positive for *S. pneumoniae* via UAD, BinaxNOW and culture, respectively. Some subjects were positive via multiple methods; 2 (0.4%) were positive via all three methods. Positive culture samples were derived from blood ($n = 15$), sputum ($n = 3$) and pleural fluid ($n = 1$).

Of 498 subjects with radiographically confirmed CAP, 51 subjects (10.2%) were positive for an identifiable *S. pneumoniae* serotype via UAD or culture. Thirty eight subjects (7.6%) were positive for PCV13 serotypes, that is, 47.5% (38 of 80) of all *S. pneumoniae* isolates identified. Twelve subjects (2.4% of all patients and 15% of the *S. pneumoniae* isolates) were positive for PCV7-associated serotypes and 26 subjects (5.2%) were positive for 1 of the 6 additional serotypes contained in PCV13 (compared to PCV7). Thirteen subjects (2.6%) were positive for non-PCV13 serotypes, and 42 (8.4% of all patients and 52.5% of all *S. pneumoniae* isolates) were presumably non-PCV13, i.e. either identified as a non-PCV13 serotype by culture (13 isolates) or detected as *S. pneumoniae* by Binax but not UAD (Fig. 2 and Table 3). Serotypes 23F (1.4%) and 6B (0.4%) were the most prevalent PCV7-associated serotypes detected, whereas serotype 3 was the most prevalent PCV13 serotype detected (2.4%). One subject had differing UAD and blood serotype results. For this subject, the UAD serotype was identified as 23F, while the blood serotype was identified as 10A. The distribution of PCV7- and PCV13-associated serotypes identified via UAD assay and culture stratified by subject characteristics is shown in Table 3.

The agreement in findings (any agreement) between UAD and culture was 90.4% (95% CI 87.3-92.9%); between UAD

Table 1. Demographics of patients with radiographically confirmed community-acquired pneumonia.

	Total n = 498 ^a	<i>Streptococcus pneumoniae</i> Status	
		Positive n = 80 ^a	Negative n = 418 ^a
Mean (SD) age, y	72.6 (10.9)	71.3 (10.8)	72.8 (10.8)
Age groups, n (%)			
50–<65 y	134 (26.9)	20 (25.0)	114 (27.3)
65–<80 y	225 (45.2)	38 (47.5)	187 (44.7)
≥80 y	139 (27.9)	22 (27.5)	117 (28.0)
Ethnicity, n (%)			
Asian	0	0	0
White	498 (100)	80 (100)	418 (100)
Black	0	0	0
Male, n (%)	310 (62.2)	50 (62.5)	260 (62.2)
Antibiotic use	393/498 (78.9)	56/80 (70.0)	337/418 (80.6)
Comorbidities, n/N (%) ^b			
None	53/498 (10.6)	11/80 (13.8)	42/418 (10.0)
Diabetes mellitus	203/498 (40.8)	30/80 (37.5)	173/418 (41.4)
Coronary artery disease	166/498 (33.3)	25/80 (31.3)	141/418 (33.7)
Chronic obstructive pulmonary disease	160/498 (32.1)	23/80 (28.8)	137/418 (32.8)
Cancer	112/498 (22.5)	17/80 (21.3)	95/417 (22.8)
Congestive heart failure	95/498 (19.1)	10/80 (12.5)	85/418 (20.3)
PPSV23 vaccine history, n (%)	249/498 (50.0)	45/80 (56.3)	204/418 (48.8)
Risk factors			
Smoking	91/498 (18.3)	15/80 (18.8)	76/418 (18.2)
Immunosuppressive therapy	48/498 (9.6)	4/80 (5.0)	44/418 (10.5)
Nursing home	5/498 (1.0)	3/80 (3.8)	2/418 (0.5)

CAP = community-acquired pneumonia; PPSV23 = 23-valent pneumococcal polysaccharide vaccine; SD = standard deviation.

^aValues are for radiographically-confirmed CAP population and *S pneumoniae*-positive or -negative subpopulations.

^bDenominators are based on the population with nonmissing values for the corresponding item and are indicated for each entry.

and BinaxNOW was 88.0% (95% CI 84.8%-90.7%); and between culture and BinaxNOW was 89.8% (95% CI 86.6%-92.4%). Agreement in finding for PCV13 serotypes between UAD and culture was 92.8% (95% CI 90.1%-95.0%).

Discussion

While *S. pneumoniae* is known to be a common cause of CAP in all age groups, this study sought to determine the serotype distribution of *S. pneumoniae* in invasive and non-invasive radiographically confirmed CAP in adults 50 years of age or older utilizing standard of care cultures, BinaxNOW, and the UAD assay. In 498 subjects with radiographically confirmed CAP in Israel, we found that 16.1% were positive for any *S. pneumoniae* serotype by ≥1 assay and 7.6% were positive for PCV13 serotypes. Serotypes 23F (1.4%) and 6B (0.4%) were the most prevalent PCV7-associated serotypes detected, whereas

serotype 3 was the most prevalent PCV13 serotype detected (2.4%).

The overall prevalence of *S. pneumoniae* in CAP in the current study was lower than results reported by Said et al in 2013 showing a proportion of CAP attributable to *S. pneumoniae* of 27%.¹⁸ While these numbers are divergent, it's important to consider that studies of CAP etiology are constrained by the sensitivity and specificity of the diagnostic assays being used. As Said and colleagues performed a meta-analysis of many other studies using different methodologies, there is a clear potential for varying results. In addition, no studies from Israel were included in the analysis by Said et al. Recent literature from LeBlanc and colleagues from hospitalized adults in Canada illustrate this. Among 4,769 all-cause CAP cases, they found that a laboratory test alone identified 14.3% as CAP related to *S. pneumoniae*.¹⁹ However, when a battery of four tests was performed (sputum culture, blood culture, a commercial pan-pneumococcal UAD, and a serotype-specific UAD), *S. pneumoniae* was identified in 23.2% of CAP cases.¹⁹ An overall

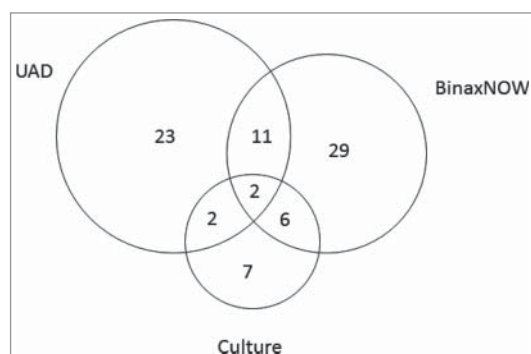


Figure 1. Identification of *S. pneumoniae* by multiple diagnostic methods. UAD = urinary antigen detection assay. *n = number of subjects with nonmissing results from ≥1 diagnostic method. Results in this figure are mutually exclusive from group to group. Total number of subjects positive for *S. pneumoniae* (n = 80).

Table 2. Overall identification of *S. pneumoniae* by diagnostic method.

	Subjects (N = 498)* <i>S. pneumoniae</i> Positive, n (%)
Any diagnostic method	80 (16.1)
UAD	38 (7.6)
UAD alone	23 (4.6)
BinaxNOW	48 (9.6)
BinaxNOW alone	29 (5.8)
Culture	17 (3.7)
Culture alone	7 (1.4)

UAD = urinary antigen detection assay.

*N = number of subjects with nonmissing results from ≥1 diagnostic method

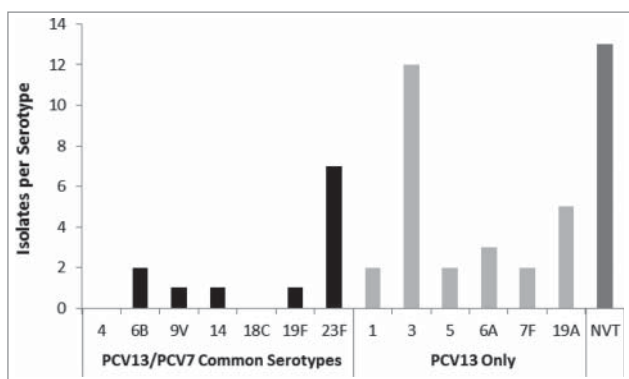


Figure 2. *S. pneumoniae* serotype distribution among isolates from *S. pneumoniae*-positive patients tested by UAD assay and culture. PCV7 = 7-valent pneumococcal conjugate vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine; NVT = non-vaccine type; UAD = urinary antigen detection.

decrease in disease as a result of a herd effect from the vaccination of children cannot be discounted however.

The diagnostic criteria used to identify CAP are also of paramount importance when looking at etiology. Data from a study conducted in Poland illustrate this by showing that among 1,195 adults with CAP, *S. pneumoniae* was detected in 12.1% of subjects.²⁰ In a subset of 1,166 subjects with radiographically confirmed CAP, *S. pneumoniae* prevalence fell to 11.2% of subjects.²⁰ Another study by Sherwin and colleagues in the United States demonstrated that 11.0% of radiographically confirmed CAP cases in adults 50 and older were related to PCV13 serotypes (note that PPSV recipients were not excluded from the analysis population).²¹ This is in contrast to our current observed prevalence of 7.6% PCV13 serotypes in adults with radiographically confirmed CAP.

Our study has several limitations that may, in part, help explain observed differences in prevalence compared to published literature. While hospital and ventilator acquired pneumonia were not to be included in the current study, the diagnosis of CAP is not without difficulty, and in addition, less severe cases of CAP not requiring hospitalization would have been missed. Antibiotic treatment prior to recruitment into the current study may also have had an effect on our results, potentially altering urinary antigen detection. We also did not check for nasopharyngeal carriage in this study; however it has been suggested that a low percentage of adult nasopharyngeal carriers will have positive urinary pneumococcal antigen detection in the absence of pneumococcal disease.²² It is not known to what extent these data can be directly extrapolated to other countries and/or populations. Additionally, the contribution of *S. pneumoniae* in the etiology of CAP varies according to the published literature and may reflect the inherent variability in study design and the sensitivity and specificity of the laboratory methods for detecting and typing pneumococci in both bacteremic and nonbacteremic CAP. In the current study three methods were employed: 1) microbiology cultures (blood, pleural fluid, bronchiolar lavage, tracheal aspirate, and respiratory culture and serotyping via Quellung reaction); 2) BinaxNOW *S. pneumoniae* test and 3) Pfizer's urine antigen detection (UAD) assay. The lack of a gold standard test to determine pneumococcal etiology in CAP makes assessment of the performance of the diagnostics challenging.^{23,24} Although highly specific, the sensitivity of microbiology cultures (blood, pleural fluid, bronchiolar lavage, tracheal aspirate, and respiratory cultures) and subsequent isolation of *S. pneumoniae* is low.^{12,18,25} Rates of positive blood cultures for adults hospitalized with pneumonia have been reported as low as 3%-8%²⁶⁻²⁸ and > 50% from those with

Table 3. PCV7 and PCV13 serotype distribution by patient demographics among isolates from patients with a positive *S. pneumoniae* isolate.

	Age Group, y 50-<65	Risk 65-<80	Pneumonia ≥80	High risk	At risk	None	HCAP	CAP
Positive isolates (any test), ^a n	20	38	22	33	36	11	n/a	n/a
Positive isolates (UAD/culture), ^b n	16	25	13	22	25	7	12	42
Total vaccine serotypes, ^c n (%)	10	18	10	12	21	5	7	31
Serotypes covered in PCV7, n (%)								
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
6B	1 (6.3)	0 (0.0)	1 (7.7)	1 (4.5)	0 (0.0)	1 (14.3)	0 (0.0)	2 (4.8)
9V	0 (0.0)	1 (4.0)	0 (0.0)	1 (4.5)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)
14	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	1 (4.0)	0 (0.0)	0 (0.0)	1 (2.4)
18C	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
19F	0 (0.0)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	1 (2.4)
23F	5 (31.3)	2 (8.0)	0 (0.0)	1 (4.5)	6 (24.0)	0 (0.0)	1 (8.3)	6 (14.3)
Total PCV7 serotypes, n (%)	6	4	2	3	7	2	2	10
6 additional serotypes in PCV13, n (%)								
1	1 (6.3)	1 (4.0)	0 (0.0)	0 (0.0)	1 (4.0)	1 (14.3)	0 (0.0)	2 (4.8)
3	1 (6.3)	8 (32.0)	3 (23.1)	4 (18.2)	6 (24.0)	2 (28.6)	0 (0.0)	12 (28.6)
5	0 (0.0)	2 (8.0)	0 (0.0)	0 (0.0)	2 (8.0)	0 (0.0)	1 (8.3)	1 (2.4)
6A	1 (6.3)	0 (0.0)	2 (15.4)	2 (9.1)	1 (4.0)	0 (0.0)	1 (8.3)	2 (4.8)
7F	1 (6.3)	1 (4.0)	0 (0.0)	1 (4.5)	1 (4.0)	0 (0.0)	1 (8.3)	1 (2.4)
19A	0 (0.0)	2 (8.0)	3 (23.1)	2 (9.1)	3 (12.0)	0 (0.0)	2 (16.7)	3 (7.1)
Total additional PCV13 serotypes, n (%)	4	14	8	9	14	3	5	21
Total non-PCV13 isolates (any test), ^a n	10	20	12	21	15	6	n/a	n/a
Typed non-PCV13 related serotypes, ^d n	6	4	3	9	2	2	3	10

CAP = community-associated pneumonia; HCAP = healthcare-associated pneumonia; PCV7 = 7-valent pneumococcal conjugate vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine; UAD = urinary antigen detection.

^aNumber of isolates identified from Binax, UAD or culture.

^bNumber of isolates identified from UAD or culture. The values in this row are used as denominators for percentages of individual serotype isolates.

^cIdentified from UAD and/or culture.

^dIdentified from culture only.

pneumococcal meningitis.²⁹ The clinically approved method for confirming and serotyping *S. pneumoniae* IPD cases has been the capsular swelling/Quellung reaction.^{30,31} This technique has relatively low sensitivity, as it requires viable bacteria in a blood sample.^{32,33} Additional potential drawbacks of this method are its reliance on technical experience and the subjective interpretation of assay results.³¹ The other two diagnostics used in this study are urine antigen detection assays. The BinaxNOW *S. pneumoniae* diagnostic tests for the presence of pneumococcal C-polysaccharide (C-PS) antigens in the urine (and in the cerebrospinal fluid of patients with meningitis) using an immunochromatographic membrane test kit. The sensitivity of this assay is documented by the manufacturer as 86% for bacteremic pneumococcal pneumonia.¹⁶ However, the sensitivity of this method has been called into question by users in the field.^{34,35} Lower sensitivity and specificity (between 52% to 82% and 83% to 97%, respectively) have been reported in studies involving adult populations with CAP.^{13-15,17} While the BinaxNOW[®] assay detects C-PS antigen, which is present in all *S. pneumoniae* strains; it does not distinguish among different pneumococcal serotypes. To this end a proprietary Luminex platform-based multiplex UAD assay that allows for the identification of 13 pneumococcal serotypes (serotypes 1, 3, 4, 5, 6A/C, 6B, 7F/A, 9V/A, 14, 18 [A, B, C, F], 19A, 19F, and 23F) in the urine of subjects with CAP was used for a more thorough investigation of serotype distribution.¹⁷ The overall validated sensitivity and specificity of this assay is reported to be 97.1% and 100%, respectively.¹⁷ While any of these individual assays could have underestimated the burden of CAP in this study, it's likely that the combination of these assays provides a better assessment of the role of *S. pneumoniae* in both bacteremic and non-bacteremic CAP.

Despite six years of high pneumococcal immunization coverage in children in Israel, we have shown that 7.6% of CAP cases among adults in Israel remain related to PCV13 serotypes; and that the burden of PCV13 may be as high as 47% of observed pneumococcal CAP.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Prior presentation

These data have not been previously presented.

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