
A Multicenter Hospital Surveillance of Invasive *Streptococcus pneumoniae*, Puerto Rico, 2001

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Although antimicrobial resistance to *Streptococcus pneumoniae* has been increased dramatically worldwide, there is limited information of pattern of susceptibility for this pathogen in Puerto Rico. Hospital-based surveillance for invasive pneumococcal infections was begun among 38 hospitals island-wide in Puerto Rico from January to December, 2001.

One hundred ninety-two cases of invasive pneumococcal disease were identified. Of the 177 isolates available for susceptibility testing, 50.3% were susceptible to penicillin and 49.7% were non-susceptible (intermediate (I) and resistance (R)) (19.2% I, 30.5% R). Resistance was documented for expanded spectrum cephalosporins and macrolides. All isolates were susceptible to vancomycin. Diabetes, cardiovascular disease, smoking and bronchial asthma were the most common risk factors associated with invasive pneumococcal disease of the adult population.

Bronchial asthma was the most common disease in the pediatric population with a fatality rate of 21%. There was no increased mortality detected among patients infected with penicillin resistant strains. Most of the isolates serotypes are represented in the 23-valent polysaccharide vaccine (78%) and 7-valent conjugate vaccine (62%). Penicillin-resistant isolates (47%) were 14, 19F, 6B, 6A, 9V, 23F, 19A and 35B serotype. Our data indicated a high prevalence for drug-resistant strains of *S. pneumoniae* in Puerto Rico. Continue surveillance for this common but serious pathogen is needed. Asthma is an important risk factor for pneumococcal disease. The pneumococcal vaccine should be recommended for all age groups with this risk factor.

Key words: Antibiotic resistance, Invasive pneumoniae, Infection, Surveillance, Puerto Rico

S*treptococcus pneumoniae* is the most common bacterial pathogen causing otitis media, sinusitis, community-acquired pneumonia and meningitis in children and adults (1). This pathogen has been the leading cause of morbidity and mortality in the United States (2). Minor degree of penicillin-resistant pneumococci strains were documented in the United States in late 1960s (3). From 1984, the reported distribution of penicillin resistant pneumococci became worldwide (4).

Although there is no evidence of active surveillance in most communities within the United States, geographic variation of penicillin-resistant *S. pneumoniae* has been reported in areas where surveillance is available and

significant increase of prevalence of resistant pneumococci has been detected (5,6). Since 1995, 14 state health departments instituted regulations for mandatory reporting of invasive *S. pneumoniae*. The Center for Disease Control and Prevention (CDC) is also sponsoring active, population-based surveillance in eight states. The latter is essential in the prevention and control of drug resistant *S. pneumoniae* (7).

Puerto Rico is a multicultural island located in the Caribbean Sea visited by thousands of people every year. The transmission of resistant pneumococcal isolates in the island has become a major concern due to the widespread dissemination of multiresistant clones worldwide. Although experience with resistant pneumococci has been commonly seen, there is no significantly large surveillance study done to document this problem in Puerto Rico. In this study we report our experience with invasive resistant pneumococcal isolates in our community and the most frequent serotypes associated with this important community-acquired pathogen.

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Methods

Hospital-based surveillance study for invasive pneumococcal disease was performed during the month of January 2001 through December 2001 in 38 hospitals throughout the island. The corresponding ethics committee of each participating hospital approved the study protocol.

The population of the surveillance area was approximately 3.8 million based on the Puerto Rico 2000 census. Hospitals invited to participate were those with more than 100 beds and/or intensive care units. Psychiatric hospitals were excluded. The percentage of hospitals participating were 75%.

Pneumococcal isolates from normally sterile sites (blood, cerebrospinal fluid, joint fluid, pleural fluid, middle ear fluid, peritoneal and bronchoalveolar lavage) were obtained from each microbiology laboratory. Collection of cultures from sterile sites followed the routine procedures established by the microbiology laboratory of each hospital. All pneumococcal isolates collected were sent to the Clendo Reference Laboratory in Bayamón, for susceptibility testing. This procedure was standardized and supervised by the authors of this manuscript. The drugs selected for susceptibility testing included penicillin, ceftriaxone, cefotaxime, chloramphenicol, clindamycin, erythromycin, trimethoprim-sulfamethoxazole, tetracycline, and vancomycin.

The inoculum suspension with turbidity equivalent to that of the 0.5 McFarland standard was prepared in 3 ml of MicroScan inoculum water with Pluronic-F, the tube was inverted, and its content transferred to a MicroScan disposable inoculum transfer device. The NCCLS control strain, *S. pneumoniae* ATCC 49619 was included in the MiCroSTREPanel to ensure the adequacy of the reagents and procedures. The susceptibility standard for each drug was defined according to the 2001 NCCLS breakpoints (8). Isolates with MICs of 0.06 µg/ml were considered penicillin susceptible, those with MICs 0.12 to 1.0 µg/ml were considered penicillin intermediate resistant and those with MICs 1.0 µg/ml were considered penicillin resistant. Non-susceptible isolates were organisms with penicillin-intermediate resistance and penicillin resistant. Pneumococcal isolates were excluded if the source of isolates was unknown, duplicate isolates from the same patient and source, and from nosocomial infections. Nosocomial infections caused by *S. pneumoniae* was defined as isolates collected 5 or more days after admission. Clinical and demographic data was collected from those patients with invasive *S. pneumoniae* disease. Pneumococcal serotyping testing was performed using the Quellung reaction method, with type-specific antiserum at the CDC, Atlanta, Georgia.

Results

One hundred and ninety-two cases of invasive pneumococcal disease were identified between January 1, 2001 and December 31, 2001. The patients ranged in age from 5 days to 96 years (mean age, 37 years); 24.5 percent of the isolates were from children less than 2 years of age, 7.3 percent from children 3 to 5 years, 6.8 percent from children 6 to 20 years, 15.1 percent from 21-48 years, 11.5 percent from 49-59 years and 29.2 percent were from 60 years and older. Fifty five percent were male and 45 percent were female. Of the 192 isolates, 156 (81.5 percent) were from blood, 10 (5.2 percent) from cerebrospinal fluid, 8 (4.1 percent) from middle ear, and 6 (3.9 percent) from blood and CSF and 4 (2 percent) from pleural and 8 (4.1 percent) from other sterile sites. No nosocomial infections were identified.

The 56.8 percent of pneumococcal infections occurred during the months of December through April. Bacteremic pneumoniae was the most common clinical syndrome associated with invasive pneumococcal disease causing 38.3% of the cases, this was followed by bacteremia without a focus (27.2%) and meningitis (10 %). Bacteremic pneumonia and bacteremia without a focus were most commonly seen in adult patients, with 69.1% and 52.1%, respectively. Table 1 describes the result of susceptibility testing. One hundred and seventy-seven (92%) of the pneumococcal isolates were available for susceptibility testing. Of these, 50.3% were susceptible to penicillin. The 19.2% had intermediate resistance and 30.5% were highly resistant to penicillin. The 23.4% of the isolates

Table 1. Antimicrobial Susceptibility Testing of Invasive Pneumococcal Infections in Puerto Rico- 2001

Antibiotic susceptible†	Susceptibility %	Intermediate %	Resistant %
Penicillin	50.3	19.2	30.5
Cefotaxime	69.5	19.8	10.7
Ceftriaxone	76.3	20.3	3.4
Erythromycin	73.4	1.1	25.4
TMP/SMX	63.1	5.1	31.8
Clindamycin	86.4	0.0	13.6
Chloramphenicol	89.8	0.0	10.2
Tetracycline	80.2	0.0	19.8
Vancomycin	100.0	0.0	0.0

* According to NCCLS 2001

† n = 177 isolates

were non-susceptible to ceftriaxone, of which 3.4% presented high-level resistance. More than 25% of the isolates were resistant to erythromycin and trimethoprim-sulfamethoxazole (TMP/SMX).

The San Juan metropolitan area, which includes the cities of San Juan, Caguas, Bayamón, Guaynabo, Carolina, Toa Baja, Cataño and Trujillo Alto, represents 30% of the total population on the island that 66.7% of the pneumococcal isolates from this area were intermediate resistant or highly resistant to penicillin; demonstrating a high prevalence of resistant pneumococci.

The most common illness associated with invasive pneumococcal disease in the pediatric population was bronchial asthma (24.4%). Those patients with an age of less than 2 years and without any other risk factors accounted for 50% of the invasive pneumococcal disease in the pediatric population. In contrast, for the adult population, the predisposing conditions were diabetes (13.8%), cardiovascular disease (13.0%), cigarette-smoking (11.6%) and asthma (8.7%). The age-range for patients with cigarette smoking history was between 39 year and 77 year of age (mean, 59.5 year). Information of the outcome of illness was missing in 29 cases (15.1%). The case-fatality rate for the surveillance population was 21%, with 60% of the deaths in patients over 60 years old. There was no increased mortality seen among patients infected with penicillin-resistant strains. Table 2 includes the most common serotypes associated with invasive pneumococcal infection and vaccine-associated serotypes in Puerto Rico.

Table 2. Invasive Pneumococcal Disease: Most Frequently Associated Serotypes. Puerto Rico, 2001

	Most frequent serotypes (in order of frequency)	% vaccine associated serotype	
		7-valent	23-valent
All Isolates n: 137	14, 19F, 6B, 6A, 9V, 4, 23F 19A, 35B, 3, 11A, 22F, 15A 18B, 1, 13, 16F, 28A, 31, 38 9N, 15B, 15C, 18F, 19C	62%	78%
0-2 years n: 31	19F, 14, 6B, 23F, 6A, 35B 11A, 4, 3	77%	
>60 years n: 42	14, 6B, 19F, 9V, 6A, 19A, 11A, 35B, 15A, 15C, 18C, 16F, 23F, 28A, 38		78%
Penicillin Resistant Isolates n: 65	14, 19F, 6A, 6B, 9V, 23F, 19A, 35B	75%	82%

n: number of isolates tested for serotypes

Discussion And Conclusions

To our knowledge, this study provides, the first hospital-based data on the prevalence of invasive *S. pneumoniae* infections in Puerto Rico. This study indicates a high prevalence of drug-resistant strains of *S.pneumoniae* in

hospitals in Puerto Rico. We consider that since the sample size was large, and includes 38 hospitals across the island, it is a representative sample of the problem in our island .

Discussion

Comparing the population in our study with that of the United States we can see that the distribution of our population does not differ significantly in gender, area of isolation or age-related invasive disease (those age < 2 years and among persons aged > 65 years) (9). Compared to mainland USA, a similarity in seasonality seems to occur in PR. Although our island has a tropical climate, there is a trend observed of this infection to occur during the most winter months of the year.

A recent multicenter study in the USA pediatric population found, central nervous system diseases, malignancies and heart disease to be the most common underlying conditions associated with invasive pneumococcal disease in children (10). Our pediatric population differs from that of USA, in that bronchial asthma was the most common underlying condition in children with invasive disease as well as the most frequent chronic disorder (Summary of the Country Chapter, Health in the Americas, Puerto Rico: Basic Country Health

Profiles, PanAmerican Health Organization, 2001). For the elderly population, up to 40% have an underlying condition associated with invasive pneumococcal disease. This addresses the importance of preventive medicine in this high risk population. Additionally, nearly 12 percent of the patients with this invasive disease were smokers, demonstrating as in the USA, that cigarette smoking can also be a the risk factor for acquired invasive pneumococcal disease in our population (11). Nuorti JP, et al. (11) reported that there was a relationship between cigarette smoking and an association with invasive pneumococcal disease among nonelderly adults. In our population, 41% of those who had a history of smoking were considered elderly (>65 years-old), this

indicates the need to reduce or avoid smoking in this population.

Compared to younger patients, our elderly patients were at a higher risk for complications (22% vs 78%) and increased mortality (11.9% vs. 88.2%). Awareness of this problem is imperative in order to encourage compliance with immunizations for those where age is the only risk

factor. Although our study was limited on the information of the immunization status of the patients with invasive pneumococcal disease, due to nature of this study, a recent CDC telephone survey documented a low prevalence of immunization for pneumococcal disease in people >65 years (24.1%) in our population (12). This information addresses the need to develop new strategies for aggressive immunization in this age groups throughout the island, with or without predisposing factors for pneumococcal disease.

In this report, we found *S.pneumoniae* as being resistant to others antibiotics beside penicillin, including macrolides and extended-spectrum cephalosporins. However, new MIC breakpoints (2002) for cefotaxime and ceftriaxone, for nonmeningeal penicillin-resistant pneumococcal isolates decreased the number of our isolates interpreted as resistant by 3.4 and 1.1, respectively.

Knowledge of susceptibility pattern for this pathogen is important in selecting antimicrobial therapy. However, the response to therapy for antibiotic resistant strains will depend on the site of infection, dose of antibiotic, and host response.

Hospital-based surveillance of community-acquired infections can provide important data for the local health department. The trends of resistance patterns in the community will impact management policy decisions. Our findings indicate that the antimicrobial resistance patterns of pneumococcal infection needs to be continually monitored.

Furthermore, we presented data on *S. pneumoniae* confirming that the 23- and 7- pneumococcal vaccine formulation could be beneficial for our community. These vaccine formulations covers a substantial proportion of the serotypes associated with the invasive disease and those isolates with resistance to penicillin. The conjugate vaccine, in development with a broader serotypes coverage, will benefit the youngest age groups and should be supported. A better immunization status will prevent complications; thereby decreasing morbidity and mortality in the high risk patients. Since our study demonstrated that bronchial asthma is an important risk factor for pneumococcal disease, vaccination should be recommended for all age groups with evidence of this risk factor.

Resumen

Aunque la resistencia antimicrobiana a *Streptococcus pneumoniae* ha aumentado dramáticamente a nivel mundial, hay poca información del patrón de susceptibilidad de este patógeno en Puerto Rico. Se comenzó en una vigilancia multicéntrica hospitalaria de

infecciones invasivas neumocócicas se comenzó en 38 hospitales a través de toda la isla comprendiendo el período de enero a diciembre de 2001. Ciento noventa y dos casos de enfermedad neumocócica invasiva fueron identificados. De las 177 cepas enviadas para pruebas de susceptibilidad, 50% fueron susceptibles a penicilina y 49.7% fueron no susceptibles (intermedia (I) y resistente (R) (19.2% I, 30.5% R). Se documentó resistencia a cefalosporinas y macrólidos. Todas las cepas fueron susceptibles a vancomicina. La diabetes, la enfermedad cardiovascular, el hábito de fumar y el asma bronquial fueron los factores de riesgo más comúnmente asociados con la enfermedad invasiva neumocócica en la población adulta; en la población pediátrica lo fue asma bronquial. La razón de mortalidad fue el 21%. No hubo aumento de mortalidad detectado entre los pacientes con enfermedad neumocócica y cepas resistente a penicilina. La mayoría de los serotipos aislados están representados en la vacuna neumocócica 23-valente polisacárido (78%) y en la vacuna neumocócica conjugada, PCV-7 (62%). Los serotipos de las cepas resistentes a penicilina (47%) fueron 14, 19F, 6B, 6^a, 9V, 23F, 19^a y 35B. Una alta prevalencia de resistencia a penicilina en cepas de *Streptococcus pneumoniae* en Puerto Rico fue documentada. El continuar la vigilancia para este común pero serio patógeno es necesario. El asma bronquial es un factor de riesgo importante para la enfermedad neumocócica y la vacuna de pneumococco debe de ser recomendada para todas las edades con esta enfermedad.

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