

**INVASIVE PNEUMOCOCCAL DISEASE AND ANTIMICROBIAL SUSCEPTIBILITY  
PATTERNS FOR *STREPTOCOCCUS PNEUMONIAE*  
LOS ANGELES COUNTY, 1996-1997**

## Background

Pneumococcal infections continue to be a leading cause of morbidity and mortality in persons of all ages. The etiologic agent, *Streptococcus pneumoniae* is the most common cause of acute otitis media, bacteremia, pneumonia, and purulent meningitis, particularly in young children, the elderly, and the immunocompromised. While a recently published Centers for Disease Control and Prevention (CDC) survey on pneumococcal vaccine coverage<sup>1</sup> found increasing vaccine coverage levels for persons 65 years (36.5%), disparities in coverage levels were found among Hispanics (24.2%) and non-Hispanic Blacks (19.7%). The currently licensed vaccine is nonimmunogenic in the most vulnerable population, infants and children under age two years.

Since the beginning of the antibiotic era in the 1940's, penicillin has been the drug of choice for treating these infections. Beginning in the 1990's, penicillin-resistant strains began to appear and data from the CDC Pneumococcal Sentinel Surveillance System for 1993-1994<sup>2</sup> showed that the prevalence of both penicillin nonsusceptible *S. pneumoniae* (PNSP; MIC  $\geq$  0.1  $\mu$ g/mL) and multiple-drug nonsusceptible (MDNSP) strains were steadily increasing, posing a serious therapeutic dilemma for clinicians. CDC active surveillance data for 1995 from eight metropolitan areas showed that prevalence of PNSP varied widely, ranging from 10% to >30% between areas and between hospitals in the same metropolitan area.

These findings support the need for local health departments to conduct surveillance for invasive pneumococcal disease. According to a telephone survey conducted by the CDC in May 1996, 15 states and one local health jurisdiction required reporting of drug-resistant *S. pneumoniae* from normally sterile sites and 12 others were planning to require reporting by June 1997.<sup>4</sup> In September 1995, the Los Angeles County (LAC) Department of Health Services, Acute Communicable Disease Control Unit began active surveillance for invasive pneumococcal disease. This report summarizes 1996-97 data on invasive pneumococcal disease and *S. pneumoniae* antimicrobial susceptibility patterns for reported cases residing in LAC (excluding the cities of Long Beach and Pasadena).

## Methods

In September 1995, active surveillance for invasive pneumococcal disease was begun as part of a pilot project to enhance reporting of selected emerging infections. One hundred eighteen reporting sites (60 percent of laboratories and hospitals in LAC) were instructed to telephone or fax reports of *S. pneumoniae* isolated from normally sterile sites utilizing a standardized case report form, and including a copy of the antimicrobial susceptibility report. Between September 1995 and July 1996, a telephone-based active surveillance system was employed to ensure completeness of reporting; calls were made bimonthly. To evaluate the sensitivity of active surveillance, 24 laboratories and 22 hospitals were randomly selected for a retrospective review of laboratory and medical records for a five-month period. In August 1996, telephone calls were replaced with an automated fax-prompt surveillance system. Data were entered into a Microsoft ACCESS database and analyzed utilizing ACCESS and SAS software. Population estimates for 1996 and 1997 were derived from the Regional

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Population Model (RPM) file developed by the County of Los Angeles Urban Research Section.

**Data Limitations**

Since surveillance data were primarily laboratory-based (74%), race/ethnicity, clinical presentation, medical risk factors, and outcome data were sparse. Antimicrobial susceptibility results were not reported in a uniform manner and susceptibility data on antibiotics other than penicillin or third-generation cephalosporins were incomplete for 1996. Also, since reporting of *S. pneumoniae* is based on a sentinel reporting system, geographic distribution of cases may be biased by report source location.

**General Descriptive Data**

A total of 1,563 case reports were received in 1996 and 1997. The same fifty-six reporting sites contributed 98% and 96% of the total reports in 1996 and 1997, respectively. We observed no significant difference in the proportion of additional cases ascertained by telephone versus by fax-prompt (9.0% versus 9.3%, p=0.8). Based on the retrospective chart review, we estimate that CDAS was able to capture 85% of cases from the participating sites.

The annual incidence of reported invasive pneumococcal disease for 1996 was 8.4 per 100,000 population (N=745), the same reported incidence recorded in 1986, the only prior year active surveillance was conducted. During 1997, the reported incidence increased 7.1% to 9.0 per 100,000 population (N=818). Most of the increase occurred in children 1-4 years of age and in individuals 75 years and older during the 1997-98 winter respiratory season, during which a new variant of influenza A (H3N1) cause widespread outbreaks. The mean male-to-female rate ratio for 1996-97 was approximately 1.06:1; the age range was 1 month to 106 years, with a median age of 48.5 years.

During 1996, invasive pneumococcal cases followed the typical seasonal pattern, peaking in late winter than gradually declining through the spring. In 1997, a similar seasonal pattern was observed; however, in December 1997, there was a dramatic 43% increase in reported cases compared to the same time period the previous year (Figure 1). This upswing in cases mirrored a Countywide outbreak of influenza that began in October 1997 and continued through the winter months.

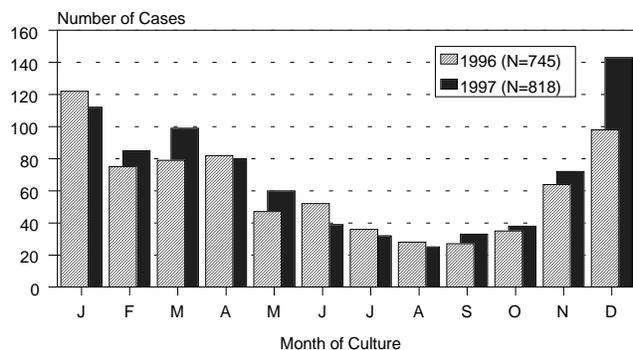
Table 1

Age-Specific Rates* of Invasive Pneumococcal Disease, Los Angeles County, 1996-1997		
Age (years)	1996	1997
<1	43.4	38.0
1-4	20.2	27.0
5-34	1.7	1.8
35-64	6.5	5.8
65-74	18.1	19.2
≥75	39.6	47.0
Overall	8.4	9.0

\* per 100,000

Figure 1

Invasive Pneumococcal Disease by Date of Culture  
Los Angeles County, 1996-1997



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The highest age-specific attack rate (AR) for 1996 occurred in infants under one year (43.4 per 100,000 population) (Table 1), followed by the 75-years-and-over age group (39.6 per 100,000) and the 1-4 year age group (20.2 per 100,000). In 1997, the highest age-specific AR was in adults 75 years and over (47.0 per 100,000); age-specific AR for infants under one year declined to 38.0 per 100,000, but increased in children 1-4 years (27.0 per 100,000).

Between 1996 and 1997, the overall case fatality rate increased 26.2% from a rate of 12.2% in 1996 to 15.4% in 1997. Calculated case fatality rates may be higher than actual rates given that outcome information was available on only 46% of cases and outcome information may more likely be recorded on cases that expire. Sixty percent of the increase in fatalities occurred among individuals 15-34 years (3.7% in 1996 compared to 12.9% in 1997), and among persons 45-64 years of age (14.3% in 1996 compared to 25.7% in 1997). Since most excess deaths occurred between October and December 1997, additional studies are planned to determine whether these excess deaths were related to the influenza outbreak.

Between 1996 and 1997, the distribution of cases by source of culture remained unchanged: 93.8% in blood only, 4.5% cerebral spinal fluid (CSF), 0.7% pleural fluid, and 1.0% from other sources such as tissue, joint fluid, peritoneal fluid, amniotic fluid, and brain cyst fluid. Case fatality rates were significantly higher for individuals with *S. pneumoniae* reported from CSF (10.1% versus 6.3%, p=0.04).

In 1996, the age-adjusted rates were highest in Harbor District (17.5 per 100,000 population) and San Fernando District (15.7 per 100,000). In 1997, the highest age-adjusted rate was in South District where the rate more than doubled from 10.2 in 1996 to 22.4 per 100,000 in 1997, followed by Antelope Valley District where the rate increased from 11.1 in 1996 to 17.6 per 100,000 in 1997. Since source of medical care is influenced by socioeconomic status, which is itself influenced by race/ethnicity, geographic distribution of reported cases is heavily biased by reporting facility. Mapping of report sources and case residences is planned to estimate disease incidence by racial/ethnic and socioeconomic group.

#### Antimicrobial Susceptibility Patterns

In 1996, susceptibility results by either minimum inhibitory concentration (MIC), E-test, or Kirby Bauer (KB) were received on 82.5% of the cases reported; the overall prevalence of penicillin-resistant *S. pneumoniae* (MIC  $\geq 0.1 \mu\text{g/mL}$ ) was 19.3% (Table 2). Of the penicillin-resistant cases with susceptibilities reported by MIC/E-test, 81.5% were penicillin-nonsusceptible (PNSP;  $\geq 0.1 \mu\text{g/mL}$ ) and 18.5% were penicillin resistant (PNR; MIC  $\geq 2.0 \mu\text{g/mL}$ ). Applying the proportion of PNSP and PNR identified by MIC/E-test to isolates reported as penicillin-resistant by KB, the prevalence of PNSP was 15.7% and PNR 3.6%. The overall prevalence of

Table 2

Proportion of Antibiotic Resistance* in Invasive Pneumococcal Isolates Los Angeles County, 1996-1997		
Antibiotic/Resistance Level	1996	1997
Penicillin, MIC $\geq 0.1 \mu\text{g/mL}$	19.3	25.8
MIC 0.1-1.0 $\mu\text{g/mL}$	(15.7)	(20.0)
MIC $\geq 2.0 \mu\text{g/mL}$	(3.6)	(5.8)
Cephalosporin, MIC $\geq 1.0 \mu\text{g/mL}$	10.4	11.4
MIC 1.0 $\mu\text{g/mL}$	(8.8)	(9.3)
MIC $\geq 2.0 \mu\text{g/mL}$	(1.6)	(2.1)

\*percent not susceptible

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third-generation cephalosporin-resistance was 10.5%: 8.8% nonsusceptible (MIC  $\geq$  1.0  $\mu\text{g/mL}$ ) and 1.6% resistant (MIC  $\geq$  2.0  $\mu\text{g/mL}$ )

In 1997, susceptibility reports were received on 84.1% of the cases reported; the overall prevalence of penicillin-resistant *S. pneumoniae* increased to 25.8%. Of the penicillin-resistant cases with susceptibilities reported by MIC/E-test, 77.5% were PNSP, and 22.5% were PNR. Applying this proportion to isolates reported by KB as penicillin-resistant, the prevalence of PNSP increased to 20.0% and of PNR to 5.8%. The overall prevalence of third-generation cephalosporin resistance also increased to 11.4%: (9.3% nonsusceptible, 2.1% resistant). Although prevalence rates for PNSP appeared generally highest in infants under one year of age, differences in prevalence rates of PNSP by age groups were not statistically significant.

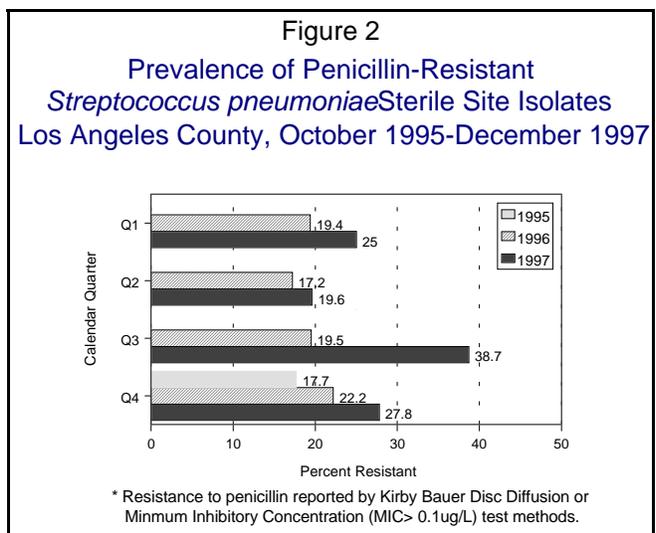
Because of the seasonal nature of this disease, for comparability of denominators, prevalence rates of penicillin-resistant *S. pneumoniae* were compared by calendar quarter. The 1995 fourth quarter prevalence rate was included for comparison purposes. As shown in Figure 2, the prevalence rates for drug-resistant cases (primarily PNSP), increased each year for each quarter.

The observed increase in the PNSP prevalence rate in the third quarter of 1997 may be due to small denominators for those months as the PNSP prevalence rate declined to more predictable levels during the fourth quarter of 1997.

Per CDC definition, isolates are classified as multiply drug-nonsusceptible pneumococci (MDNSP) if MICs are at or above the intermediate break point for two or more of the following antibiotic classes;  $\beta$ -lactams and carbapenems (penicillin, cefotaxime, imipenem), trimethoprim-sulfamethoxazole (TMP-SMZ), macrolides (erythromycin), ofloxacin, tetracyclines, or chloramphenicol. A MDNSP prevalence rate of 12.6% was reported by the CDC Sentinel Surveillance System 1993-1994.<sup>2</sup> In 1997, local susceptibility data on two or more antibiotic classes were provided on 75.9% (522/688) of LAC reports with antimicrobial susceptibility results (MIC or KB); the prevalence of MDNSP was 14.6%. Since data on the level of resistance (nonsusceptible vs. resistant) for antibiotics other than penicillin and third-generation cephalosporins were sparse, only overall antibiotic-resistance prevalence rates were calculated for the following antibiotics: cefotaxime (12.7%), TMP-SMZ (23.1%), erythromycin (9.7%), ofloxacin (16.6%), tetracycline (43.1%), chloramphenicol (9.4%). All isolates tested were susceptible to vancomycin.

### Discussion

The increasing prevalence of PNSP in Los Angeles County and appearance of MDNSP strains in other health jurisdictions, underscores the importance of continuing surveillance for invasive pneumococcal disease and monitoring of *S. pneumoniae* resistance



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patterns. The current surveillance system can be improved by requiring uniform reporting of susceptibility results to include MIC results for each of the six major antibiotic classes defined by the CDC. Additional studies are necessary to : (1) determine whether reporting sites are representative of the County population as a whole, (2) estimate race/ethnicity and socioeconomic status of cases, (3) better ascertain case fatality rates, (4) describe clinical presentation of cases, and (5) determine whether there are geographic differences in the prevalence of PNSP and MDNSP in LAC.

#### References

1. CDC. Pneumococcal and influenza vaccination levels among adults aged  $\geq 65$  years -- United States 1995. *MMWR*;46(39).
2. Butler JC, Hoffman J, Cetron MS, Elliot JA, Facklam RR, Breiman RF. Pneumococcal Sentinel Surveillance Working Group. The continued emergence of drug-resistant *Streptococcus pneumoniae* in the United States: an update from the Centers for Disease Control and Prevention's Pneumococcal Sentinel Surveillance System. *J Infect Dis* 1996;1274:986-993.
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