CLINICAL PRACTICE

Antibiotic Surveillance of *Streptococcus pneumoniae* in Mississipi

HEATHER W FLOWERS, DONNA C SULLIVAN, THOMAS B WIGGERS, ANNE WHITEHURST

OBJECTIVE: A survey of antimicrobial resistance in *S. pneumoniae* isolates collected from representative geographic regions of Mississippi during two different respiratory seasons was conducted to determine rates and distribution of drug resistance.

DESIGN: A total of 318 *S. pneumoniae* isolates was collected from July 1999 to March 2000, and 171 isolates were collected from July 2001 to March 2002. The minimum inhibitory concentration for 12 antibiotics was determined by the micro dilution method.

SETTING: A total of 28 hospitals through out the state of Mississippi participated in the submission of *S. pneumoniae* isolates felt to be clinically relevant and reported to the attending physician. Specimens were transported to a central laboratory via state health department courier.

PATIENT POPULATION: Isolates were obtained from hospital inpatients as well as outpatients seen in local clinics.

MAIN OUTCOME MEASURES: Changes in the percentage of isolates resistant to the tested antibiotics and patient demographics were collected.

RESULTS: Pediatric isolates accounted for 36% and 28%, respectively, in 2000 and 2002. The relative percentage of total respiratory isolates remained for each year. Resistance to penicillin increased in pediatric (58% vs. 71%) and adult (40% vs. 52%) as did resistance to ceftriaxone (pediatric 14% vs. 31%; adult 9% vs. 25%) from 2000 to 2002. The majority of isolates were resistant to multiple antibiotics in both years tested.

CONCLUSION: The results of this study are comparable to those from other national studies of antimicrobial resistance in *S. pneumoniae* demonstrating increasing resistance to multiple classes of antibiotics quantitatively and qualitatively.

ABBREVIATIONS: AMOX = amoxicillin; AZITH = azithromycin; BAL = bronchioalveolar lavage; CFX = cefuroxime; CLIND = clindamycin; CLSI = Clinical and Laboratory Standards Institute, formerly NCCLS; CSF = cerebrospinal fluid; CTX = ceftriaxone; LEVO = levofloxacin; NP = nasopharynx; PCN = penicillin; TETRA = tetracycline.

INDEX TERMS: antibiogram; antibiotic resistance; antibiotic sensitivity; pneumococci; pneumonia; S. pneumoniae.

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Antibiotics, originally hailed as "miracle drugs", are widely prescribed, often inappropriately. In response to this attack, bacteria have evolved mechanisms of resistance to almost all classes of these drugs. Due to the nature of both the patient population and the physical environment, most concerns about resistance have focused primarily on hospitals, with only limited attention paid to family physicians and outpatient settings.[1] Antimicrobial resistance has spread to all communities and all healthcare settings, resulting in new diagnostic challenges, complicated therapeutic choices, and increasing treatment cost as well as rising patient morbidity and mortality.[1]

S. pneumoniae is a leading cause of morbidity and mortality worldwide.[2,3] It is the most common cause of community-acquired pneumonia, bacterial meningitis, and acute otitis media.[4,5] Initially, all *S. pneumoniae* isolates were

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susceptible to penicillin and β-lactams served as the treatment of choice.[6,7,8] In the 1960's, resistance to penicillin and other antimicrobials began to be reported and drug-resistant *S. pneumoniae* is now recognized worldwide.[2,9,10,11,12,13,14,15] Recent surveillance surveys in the United States have shown penicillin resistance to range anywhere from 15% to >50%.[8,14,16,17] The wide range in resistance rates reflect different geographical areas as well as differing risk factors such as age and race.[18] Well-documented cases of multidrug resistance to penicillins, macrolides, sulfonamides, and third generation cephalosporins have been reported.[19,20,21] Coupled with the increasing proportion of these strains in community-acquired infections, the importance of local surveillance is crucial when choosing initial empiric therapy for infections in which *S. pneumoniae* may be present. We conducted a survey of antimicrobial resistance in *S. pneumoniae* isolates collected from representative geographic regions of Mississippi during two different respiratory seasons. This study is the first comprehensive, statewide survey of *S. pneumoniae* resistance in Mississippi and provides important observations on antimicrobial resistance in a predominantly rural region.

METHODS

Collection and storage of isolates: The collection of *S. pneumoniae* isolates from clinically ill individuals was instituted following solicitation of participation by letter, phone, and e-mail contact. Each of 28 hospitals which participated was asked to submit every *S. pneumoniae* isolate reported to the attending physician which was felt to be clinically relevant. A total of 318 *S. pneumoniae* isolates were collected from July 1999 to March 2000, and 171 isolates were collected from July 2001 to March 2002. The isolates were obtained from both hospital inpatients as well as outpatients seen in local clinics. Specimens were received on transport media via state health department courier and were grown on trypticase soy agar with 5% sheep blood (TSA) to assure viability. Colonies were then streaked for isolation on TSA and incubated for 20-24 hours in 5% CO_2. Isolated colonies were picked and inoculated into Todd-Hewitt broth and grown to mid-log phase, at which point glycerol was added to 20% final concentration and the culture was stored at –80° C.

Analysis of minimum inhibitory concentrations: Determination of antimicrobial susceptibilities followed Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) guidelines.[22] Frozen stock cultures were grown on TSA for 20-24 hours in 5% CO_2. *S. pneumoniae* colonies were swabbed off the plates and resuspended in saline to a 0.5 McFarland standard. Microtiter 96-well plates were prepared by PML Microbiologicals (Portland, OR) according to CLSI criteria for broth micro dilution testing of *S. pneumoniae*. Wells were inoculated with 10^5 bacterial cells and incubated for 20-24 hours at 35° C. A total of 12 antimicrobial agents—penicillin, amoxicillin, ceftriaxone, cefuroxime, azithromycin, clindamycin, tetracycline, trimethoprim-sulfamethoxazole,

Table 1. Demographics of analyzed *S. pneumoniae* isolates

	2000		2002		Total
Total isolates*	318		171		484
Male	168		89		257
Female	150		73		223
Adult	204		118		322
Pediatric	114		48		162
Respiratory	**Adult**	**Ped**	**Adult**	**Ped**	
BAL	7	0	3	0	10
Bronchoscopy	4	1	7	1	13
Nose	1	9	0	0	13
NP	4	26	3	18	51
Sinus	6	9	2	5	22
Sputum	97	3	56	1	157
Pleural fluid	3	0	1	0	4
Non-respiratory					
Blood	68	25	31	6	130
CSF	3	2	2	0	7
Ear	2	31	4	12	49
Eye	2	7	3	3	15
Misc.	2	0	2	0	4

Abbreviations: BAL = bronchial alveolar lavage; CSF = cerebrospinal fluid; NP = nasopharynx.
*Complete demographic data were not available for all isolates.

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levofloxacin, gatifloxicin, moxifloxacin, and vancomycin—were included for testing. These antibiotics were chosen for analysis because of their extensive use as well as indications for treatment. Gatifloxicin and moxifloxacin were included as newer agents for streptococcal infections. Minimal inhibitory concentrations (MIC) were determined by the lowest concentrations of antibiotic which inhibited visible growth. *S. pneumoniae* ATCC strain 49619 was used as a control and MICs for this strain were all within specified ranges.

RESULTS

During the 2000 respiratory season 318 isolates were collected, while 171 isolates were collected in 2002. Demographic data and site of isolation are seen in Table 1. Complete demographic data (sex, age) were not available for all isolates. Pediatric isolates (defined as $\leq$ 5 years of age) accounted for 36% and 28%, respectively, in 2000 and 2002. The relative percentage of total respiratory (sputum, nasopharynx, sinus, or bronchial alveolar lavage) isolates remained the same from the 1999-2000 and 2001-2002 season (54% vs. 60%). The majority of respiratory isolates were from the adult population (57% each year). In 1999-2000, 46% of *S. pneumoniae* isolates were non-respiratory: from blood, cerebrospinal fluid, pleural fluid, and synovial fluid. The overall percentage of non-respiratory isolates did not change substantially in 2001-2002 (40%). Non-respiratory isolates from the pediatric population were predominantly from the ear: 31/65 isolates in 2000 and 12/21 isolates in 2002.

Twelve antibiotics were tested for each isolate: penicillin, amoxicillin, ceftriaxone, cefuroxime, azithromycin, clindamycin, tetracycline, trimethoprim-sulfamethoxazole, levofloxacin, gatifloxicin, moxifloxacin, and vancomycin. These were chosen to represent oral and parental classes of antimicrobials suggested for testing against *S. pneumoniae* by the CLSI. Some newer fluoroquinolones were also included because they have been developed and are marketed, in part, for their increased gram-positive activity. Susceptibilities for each antibiotic are shown in Table 2 and are divided into sensitive, intermediate, and resistant categories as defined by the CLSI.[22] Results for pediatric and adult isolates are shown in Figure 1. For simplicity in the figure and the following discussion, intermediate and resistant will be combined and referred to as clinically resistant. Antibiotics with intermediate sensitivities are generally considered inappropriate standard of care and are grouped together with true microbiological resistance as clinically resistant.

For the respiratory season of 2000, the overall rate of clinically relevant penicillin resistance (combined intermediate and high levels) was 47%. Penicillin resistance in pediatric isolates was 58% in 2000 compared to 71% in 2002. Adult isolates had penicillin resistance levels of 40% and 52% in 2000 and 2002, respectively. Pediatric isolates were more likely to be resistant to amoxicillin (32% and 22% in 2000 and 2002, respectively) than adult isolates (18% and 16%

Table 2. Comparative antibiotic sensitivities for 2000 and 2002

ANTIBIOTIC	SENSITIVE		INTERMEDIATE		RESISTANT	
	2000	2002	2000	2002	2000	2002
Penicillin	170 (53%)	71 (42%)	72 (23%)	45 (26%)	76 (24%)	55 (32%)
Amoxicillin	246 (77%)	140 (82%)	26 (8%)	19 (11%)	46 (15%)	12 (7%)
Ceftriaxone	284 (90%)	121 (71%)	17 (5%)	31 (18%)	17 (5%)	19 (11%)
Cefuroxime	188 (59%)	90 (53%)	16 (5%)	15 (8%)	114 (36%)	66 (39%)
Azithromycin	172 (54%)	72 (42%)	7 (2%)	7 (4%)	139 (44%)	92 (54%)
Clindamycin	299 (94%)	143 (84%)	1 (<1%)	4 (2%)	18 (6%)	24 (14%)
Tetracycline	266 (84%)	140 (82%)	2 (<1%)	0 (0%)	50 (16%)	31 (18%)
TMP/SMX	160 (50%)	72 (42%)	6 (2%)	9 (5%)	152 (48%)	90 (53%)
Levofloxacin	318 (100%)	170 (99%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)
Gatifloxcin	316 (99%)	171 (100%)	0 (0%)	0 (0%)	2 (<1%)	0 (0%)
Moxifloxacin	316 (99%)	171 (100%)	2 (<1%)	0 (0%)	0 (0%)	0 (0%)

Number of isolates is followed by percent of total isolates in parentheses.

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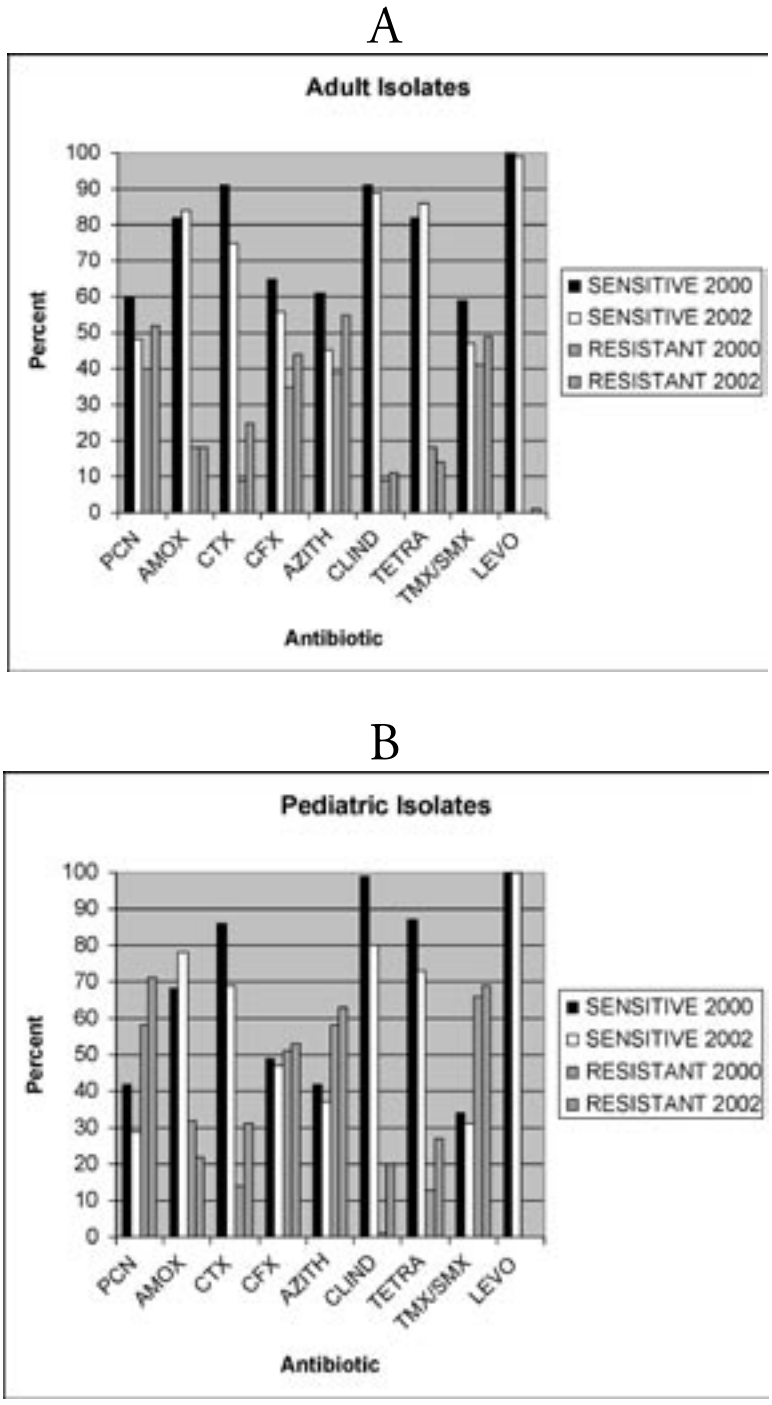
Figure 1. Comparison of *S. pneumoniae* isolates from pediatric patients (panel A) and adult patients (panel B)



Abbreviations: AMOX = amoxicillin; AZITH = azithromycin; CFX = cefuroxime; CLIND = clindamycin; CTX = ceftriaxone; LEVO = levofloxacin; PCN = penicillin; TETRA = tetracycline.

in 2000 and 2002, respectively). For pediatric isolates, ceftriaxone resistance was 14% and 31% while the macrolide azithromycin had resistance levels of 58% and 63%, for 2000 and 2002. In contrast, adult isolates, resistance to ceftriaxone was 9% in 2000 and increased to 25% in 2002. Azithromycin resistance in adult isolates was 39% in 2000, increasing to 55% in 2002. *S. pneumoniae* isolates from pediatric patients resistance levels to tetracycline was 13% in 2000, increasing to 27% in 2002. Adult isolates had tetracycline resistance levels of 18% and 14% in 2000 and 2002, respectively. Trimethoprim-sulfamethoxazole resistance levels were 66% and 69% in pediatric isolates and 41% and 53% for adult isolates, 2000 and 2002 respectively. There was no substantial resistance to the fluoroquinolones, levofloxacin, gatifloxcin and moxifloxacin, in either pediatric or adult isolates.

Multidrug resistance was observed in both pediatric and adult populations. As shown in Figure 2, all of the isolates collected in 2000 were clinically resistant to at least two antibiotics and 48% of the isolates were resistant to at least four antibiotics. Multidrug resistant isolates were found throughout the state, in both rural areas as well as the more heavily populated regions in central Mississippi and along the Gulf Coast. In 2002, this trend reversed itself somewhat with 34% of the total isolates collected susceptible to all antibiotics tested. However, 41% of the total isolates collected in 2002 remained resistant to at least four antibiotics. There was no difference in rural vs. urban or adult vs. pediatric among the susceptible isolates.

CONCLUSIONS

Antimicrobial surveillance has been defined as a systematic collection and

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analysis of data that can be used to identify resistance trends.[23] Both the Centers for Disease Control and Prevention and the American Society for Microbiology task force have stressed the importance of antimicrobial surveillance at the local, national, and global level.[21,24] While regional, national, and global data may indicate the magnitude of resistance to a given drug, local and institutional data may be of greater importance to clinicians when managing patients.[25,26] In order to identify resistance trends within our state, we compared data collected for two respiratory seasons for *S. pneumoniae*.

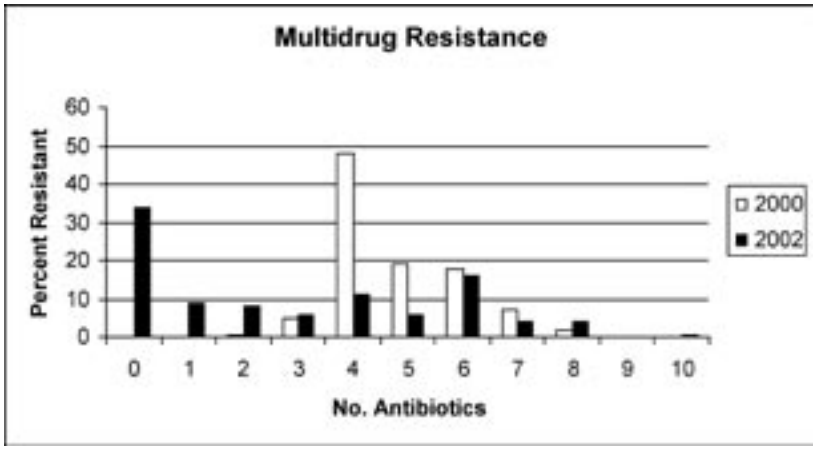
During the last two decades, the penicillin resistance rates of *S. pneumoniae* have increased dramatically. Combined data from 33 centers in the US (1999-2000) indicated an overall (adult and pediatric isolates) penicillin resistance rate of 34.2% with a 42.6% rate in pediatric isolates.[8] Substantially higher rates were observed in this study: 47% and 58% overall vs. 58% and 71% for pediatric isolates, 2000 and 2002, respectively. *S. pneumoniae* is the most important bacterial pathogen in children and adolescents, accounting for approximately 40% to 50% of cases of bacterial meningitis, acute otitis media, acute sinusitis, and pneumonia; 90% of cases of occult bacteremia in infants and toddlers who have fever without an obvious focus of infection; many cases of septicemia; and, sometimes, rapidly fatal disease in individuals with absent or impaired splenic function, abnormal humoral or cellular immunity, or compromised phagocytic cell function. [29] Thus, the rate of resistance in pediatric populations is especially troubling.

Pediatric populations are at increased risk for *S. pneumoniae* for several reasons. Day care attendance may increase a child's risk of invasive pneumococcal disease both directly and indirectly. Children attending day care centers come from different homes and it is likely that they are exposed to a greater number of pneumococcal serotypes. Also, children who attend day care may be exposed to a greater inoculum of pneumococci than are children who do not attend day care because of the intensity of contact that occurs in day care centers.[30]

Resistance to cephalosporins usually occurs in a pattern parallel to penicillin, with ceftriaxone resistance reported at 24.7% overall in national surveys in 1999-2000 [8]. In our survey, ceftriaxone resistance was similar to that reported nationally: overall, 10% and 27%, 2000 and 2002, respectively. However, there was not a close parallel between penicillin and cephalosporin resistance in this study, as has been reported by others. Penicillin resistance increased substantially in Mississippi from 2000 to 2002 while ceftriaxone resistance, although increasing, remained similar to national levels.

Macrolide resistance has been reported nationally to vary from 25% to 54%.[8] In this study, resistance to the macrolide azithromycin overall was 46% in 2000 and 57% in 2002, with rates slightly higher in pediatric populations as described above (Figure 1). Of the two common mechanisms of macrolide resistance, one (*ermB* ribosomal methylase gene) is also associated with resistance to the lincosamide clindamycin.[8,27] In this study, clindamycin resistance was very low, 6% and 14% overall for 2000 and 2002. This data suggests that macrolide resistance in our population may be more likely due to an efflux mechanism controlled by the *mefA* gene.[8,27] Conclusive proof would require molecular analysis of these two genes and is beyond the scope of this survey. Resistance to macrolides, tetracycline, and trimethoprim/sulfamethoxazole can be associated with penicillin resistance but may occur independently.[8,27] Here,

Figure 2. Comparison of multi-drug resistance rates



The number of antibiotics to which an isolate was resistant is shown on the X axis; the Y axis shows the percentage of total isolates with resistance. Data is shown from each year of collection.

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we report similar levels of resistance for penicillin and trimethoprim/sulfamethoxazole but low levels of tetracycline resistance (Table 2, Figure 1).

The results of this study are comparable to those from other national studies of antimicrobial resistance in *S. pneumoniae*.[10,13] *S. pneumoniae* resistance to multiple classes of antibiotics is increasing both quantitatively and qualitatively. This study is notable for its comprehensive scope during two respiratory seasons in a largely rural region. Most national surveys of *S. pneumoniae* resistance include selected urban area tertiary-care hospitals. As reported by Schrag and colleagues, very high-level penicillin resistant pneumococci were identified in California, Minnesota, Tennessee, and Georgia in 1995, with Tennessee having the highest rate.[28] Mississippi is predominantly a rural state with major population centers located in the Jackson area in the central region of the state (State Health District 5) and along the Gulf Coast (State Health District 9). These two major population centers provide healthcare for a large part of the rural, medically underserved regions. In 2000, all *S. pneumoniae* isolates were resistant to at least two antibiotics, demonstrating that high-level antimicrobial resistance has penetrated rural areas as well as large cities in the US. It is also interesting to note that there is substantial regional variation within Mississippi. Somewhat unexpectedly, rural areas had higher resistance rates than the largest metropolitan area of the state. Of the fully susceptible isolates obtained in 2002, the majority, 59%, were from the major population centers, indicating that resistance remained a problem in rural areas.

Considering all the agents tested, there were higher than expected rates of resistance to macrolides and trimethoprim-sulfamethoxazole. In contrast, the rate of resistance to third generation cephalosporins (e.g., ceftriaxone) was lower than that reported for surrounding regions and lower than what would be predicted from the high rate of penicillin resistance.

The increasing prevalence of antimicrobial resistance is a concern for all healthcare providers. National medical organizations such as the Infectious Diseases Society of America have expressed concern over this growing problem. Millions of prescriptions are written each year by physicians, regardless of their specialty. It is estimated that 20% to 50% of these prescriptions in community settings are unnecessary.[1] Although many national and international surveillance programs have been introduced to track the scope and magnitude of the problem, no provisions are currently made for such programs on a statewide basis in Mississippi.[26] In a predominantly rural state such as ours, collection of data from regional referral centers may be particularly important for empirical therapy and changes in prescribing practices.

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