Mortality From Invasive Pneumococcal Pneumonia in the Era of Antibiotic Resistance, 1995–1997

ABSTRACT

Objectives. This study examined epidemiologic factors affecting mortality from pneumococcal pneumonia in 1995 through 1997.

Methods. Persons residing in a surveillance area who had community-acquired pneumonia requiring hospitalization and *Streptococcus pneumoniae* isolated from a sterile site were included in the analysis. Factors affecting mortality were evaluated in univariate and multivariate analyses. The number of deaths from pneumococcal pneumonia requiring hospitalization in the United States in 1996 was estimated.

Results. Of 5837 cases, 12% were fatal. Increased mortality was associated with older age, underlying disease, Asian race, and residence in Toronto/Peel, Ontario. When these factors were controlled for, increased mortality was not associated with resistance to penicillin or cefotaxime. However, when deaths during the first 4 hospital days were excluded, mortality was significantly associated with penicillin minimum inhibitory concentrations of 4.0 or higher and cefotaxime minimum inhibitory concentrations of 2.0 or higher. In 1996, about 7000 to 12 500 deaths occurred in the United States from pneumococcal pneumonia requiring hospitalization.

Conclusions. Older age and underlying disease remain the most important factors influencing death from pneumococcal pneumonia. Mortality was not elevated in most infections with β-lactam–resistant pneumococci. (*Am J Public Health*. 2000;90:223–229)

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At the turn of this century, Osler claimed that "the most widespread and fatal of all acute diseases, pneumonia, is now the Captain of the Men of Death."[1] In the United States, pneumonia is still a major cause of mortality, and *Streptococcus pneumoniae* is the leading cause of community-acquired pneumonia.[2–5] Mortality from pneumococcal pneumonia has remained high despite the introduction of antibiotics and improved intensive care medicine.[5–8] In recent studies, the case-fatality rates for bacteremic pneumococcal pneumonia ranged from 7% to 35%.[5,8–12]

The prevalence of antibiotic-resistant *S pneumoniae* has increased over the last decade in the United States. The proportion of pneumococci nonsusceptible to penicillin has reached 35% in some areas.[13,14] Along with the rise in antibiotic resistance, questions about its clinical impact have been raised. Worse outcomes in cases of meningitis caused by resistant pneumococci have been documented.[15–17] However, in cases of pneumonia caused by resistant pneumococci, worse outcomes have not been clearly shown.

We report the results of population-based, active surveillance for invasive *S pneumoniae* disease from 9 geographic areas in North America. We focus on epidemiologic factors affecting mortality, including antibiotic resistance, and estimate the number of annual deaths in the United States from pneumococcal pneumonia.

Methods

The surveillance areas were San Francisco County, Calif, 8 counties in Georgia, 6 counties in Maryland, 5 counties in Tennessee, and metropolitan Toronto/Peel, Ontario (January 1, 1995, through December 31, 1997); the entire state of Connecticut (March 1, 1995, through December 31, 1997); 7 counties in Minnesota (April 1, 1995, through December 31, 1997); 3 counties in Oregon (July 1, 1995, through December 31, 1997); and Bexar County, Tex (January 1, 1995, through August 31, 1996). Two additional counties from California were included from January 1, 1995, through September 30, 1995.

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The Georgia site later added 12 more counties (January 1, 1997, through December 31, 1997). The maximum surveillance population was 22 149 215. Blacks represented 17% of the surveillance population (excluding Toronto/Peel) compared with 13% of the US population.

Invasive pneumococcal disease was defined as isolation of *S pneumoniae* from a normally sterile site, such as blood, cerebrospinal fluid, or pleural fluid, in a person residing in a surveillance area. A case was defined as pneumonia if the chart abstractors found evidence of pneumonia in the medical record (i.e., *International Classification of Diseases, 9th Revision* [ICD-9 code],[18] positive x-ray, or documented impression of the clinician) and as meningitis if the cerebrospinal fluid grew *S pneumoniae*.

The outcome of each episode of invasive *S pneumoniae* was determined by review of medical records. Patients discharged from the hospital were considered to have survived. To improve the chance that deaths were due to pneumococcal infection rather than other causes, deaths after 30 days in the hospital were excluded from the analysis of pneumonia deaths. For the purposes of this analysis, a case was considered nosocomial if the collection date of the specimen from which *S pneumoniae* was isolated was 2 or more calendar days after admission.

The surveillance methods were described previously.[19] The susceptibility standards for each antibiotic were defined according to the 1998 National Committee for Clinical Laboratory Standards.[20] Resistance to penicillin was defined as a minimum inhibitory concentration (MIC) of 2.0 μg/mL or higher, and intermediate susceptibility was defined as an MIC of 0.12 to 1.0 μg/mL. Resistance to cefotaxime was defined as an MIC of 2.0 μg/mL or higher, and intermediate susceptibility was defined as an MIC of 1.0 μg/mL. The term *nonsusceptible* refers to both resistant and intermediate organisms.

Statistical analysis was performed with SAS (Version 6.12; SAS Institute, Inc, Cary, NC) and Epi Info (Version 6.03; Centers for Disease Control and Prevention, Atlanta, Ga). The χ^2 test and the Fisher exact test were used to compare proportions. Age adjustments for case-fatality rates were done via the direct method, with the pooled number of invasive pneumococcal cases for the following age categories used as the standard population: 0 to 17 years, 18 to 64 years, and 65 years or older. A previously defined technique[21] was used to compare age-adjusted rates. Estimates of deaths from pneumococcal pneumonia were age- and race-adjusted from the population of the surveillance areas participating during the entire calendar year of 1996, excluding Toronto/Peel, to the US population as estimated by the US Census Bureau in 1994, the most recent year for which figures were available at the county level. Race adjustments were performed by categorizing race as Black and non-Black.

Unconditional logistic regression was used to evaluate factors resulting in increased mortality from invasive pneumococcal pneumonia. The initial model included demographic variables considered to be important influences on mortality (Table 1). Information on underlying diseases was collected from certain geographic areas only. Underlying disease status was dichotomized into having a condition thought to contribute to increased mortality from invasive pneumococcal infection and having none of these conditions (Table 2).[22] Based on previous studies, asthma and HIV infection without AIDS were included in the "no underlying disease" category.[6,10,23,24]

In evaluating the effect of antibiotic resistance on mortality, we excluded pneumonia patients who also had meningitis. In the logistic regression models evaluating the effect of antibiotic resistance, we included only patients from the 4 geographic areas where information on underlying disease and antibiotic MICs was available: Maryland,

TABLE 1—Demographic Characteristics and Case-Fatality Rates (CFRs) of Persons Hospitalized With Community-Acquired, Invasive Pneumococcal Pneumonia Requiring Hospitalization, 1995–1997

	n (% of Total[a])	No. of Deaths (Unadjusted CFR)	Age-Adjusted CFR	*P*[b]
Age, y				
<2	171 (3)	6 (4)	. . .	.33
2–17	241 (4)	4 (2)	. . .	Reference
18–49	2087 (36)	160 (8)	. . .	<.001
50–64	936 (16)	102 (11)	. . .	<.001
65–74	895 (15)	114 (13)	. . .	<.001
75–84	892 (15)	170 (19)	. . .	<.001
≥85	583 (10)	135 (23)	. . .	<.001
Sex				
Female	2688 (46)	322 (12)	13	Reference
Male	3113 (54)	369 (12)	11	.062
Race/ethnicity				
Asian	105 (2)	22 (21)	25	<.001
Black	1467 (28)	129 (9)	10	.21
White	3276 (62)	452 (14)	12	Reference
Unknown/other	452 (9)	61 (13)	13	.34
Hispanic[c]	250 (4)	28 (11)	13	.76
Geographic area				
California	597 (10)	74 (12)	14	.25
Connecticut	1207 (21)	159 (13)	12	Reference[d]
Georgia	615 (11)	71 (12)	12	.86
Maryland	985 (17)	80 (8)	9	.0056
Minnesota	493 (9)	45 (9)	10	.11
Oregon	326 (6)	39 (12)	11	.55
Tennessee	744 (13)	85 (11)	12	.61
Texas	202 (3)	23 (11)	12	.74
Toronto/Peel	636 (11)	115 (18)	16	.020
Pneumonia complications				
Uncomplicated pneumonia	5709 (98)	675 (12)	11	Reference
Meningitis	46 (1)	10 (22)	26	.0091
Positive pleural fluid culture	127 (2)	9 (7)	9	.42
Underlying disease				
Absent	898 (38)	46 (5)	7	Reference
Present	1478 (62)	261 (18)	17	<.001

[a]Totals for each demographic characteristic vary because of missing data. Cumulative percentages may not equal 100 because of rounding.
[b]*P* for age groups calculated with the χ^2 test. For other demographic characteristics, *P* calculated by comparison of age-adjusted CFRs between each demographic factor and referent demographic factor for that category.[21]
[c]Patients of Hispanic ethnicity could also be classified into another race category. Age-adjusted CFRs for Hispanics were compared with those of patients self-identified as non-Hispanic.
[d]Connecticut was considered the reference area because it had the median age-adjusted CFR.

TABLE 2—Case-Fatality Rates (CFRs) of Hospitalized Persons With Various Underlying Diseases[a] From Community-Acquired, Invasive Pneumococcal Pneumonia Requiring Hospitalization, 1995–1997

Underlying Disease	No. of Deaths / Total (Unadjusted CFR)	Relative Risk (95% Confidence Intervals)
None	44 / 757 (6)	Reference
Liver cirrhosis	20 / 59 (34)	5.8 (3.7, 9.2)
Congestive heart failure	70 / 255 (27)	4.7 (3.3, 6.7)
Renal failure[b]	40 / 164 (24)	4.2 (2.8, 6.2)
Cancer (solid organ)	45 / 210 (21)	3.7 (2.5, 5.4)
Atherosclerotic heart disease	29 / 156 (19)	3.2 (2.1, 5.0)
Asplenia	3 / 16 (19)	3.2 (1.1, 9.3)
Diabetes mellitus	43 / 254 (17)	2.9 (2.0, 4.3)
Chronic obstructive pulmonary disease	60 / 372 (16)	2.8 (1.9, 4.0)
Immunosuppressive therapy	23 / 157 (15)	2.5 (1.6, 4.1)
AIDS	28 / 207 (14)	2.3 (1.5, 3.6)
Hematologic malignancy	10 / 77 (13)	2.2 (1.2, 4.3)
Asthma	12 / 159 (8)	1.3 (0.7, 2.4)
HIV infection (without AIDS)	13 / 206 (6)	1.1 (0.6, 2.0)

[a]Patients may have more than 1 underlying disease. Georgia, Tennessee, and Oregon were excluded because they did not collect information on underlying disease. From other states, only cases in which information about underlying disease was available were included.
[b]Defined as requiring dialysis or having nephrotic syndrome.

Texas, California, and Toronto/Peel. Logistic regression models evaluating the association between antibiotic resistance and mortality adjusted for age, race, geographic area, and underlying disease. Because deaths within the first few hospital days may reflect the severity of presenting illness rather than the result of treatment failure, additional regression models were performed that excluded deaths during the first 2 and 4 hospital days.

Results

A total of 12 194 cases of invasive *S pneumoniae* disease were identified during the surveillance period; 6570 (54%) cases were pneumonia. The percentage of invasive disease classified as pneumonia was 20% in patients younger than 18 years, 58% in those 18 to 64 years, and 70% in those older than 65 years. *S pneumoniae* was isolated from the blood in 6446 (98%) of all the pneumonia cases and from the pleural fluid in 127 (2%). Of the 6570 pneumonia patients, 6034 (92%) were admitted to or were already in the hospital at the time the culture was collected. Of the 6034 hospitalized patients, 5837 (97%) had community-acquired pneumonia. The age-adjusted case-fatality rate for nosocomial cases (28%) was significantly higher than that for community-acquired cases (12%, $P < .001$), even after adjustment for the presence of underlying disease.

Of the 5837 cases of community-acquired, invasive pneumococcal pneumonia requiring hospitalization, 723 patients died, yielding an overall case-fatality rate of 12%. The mean time from date of admission to death was 8 days (median, 4 days; range, 0–107 days). Nine percent of the patients with fatal cases died on the day of hospital admission, and 21% died on the second hospital day. Thirty-two (4%) of the deaths occurred after 30 days in the hospital. The demographic characteristics of patients hospitalized with community-acquired, invasive pneumonia are shown in Table 1.

The case-fatality rate for community-acquired, invasive pneumococcal pneumonia requiring hospitalization was significantly elevated for patients who were older, Asian, and Toronto/Peel residents or who had meningitis (Table 1). Mortality was lowest among Maryland residents. In addition, the case-fatality rate was significantly higher among those with a severe underlying disease, although it differed substantially depending on the illness (Table 2). In a logistic regression model, increased mortality from invasive pneumococcal pneumonia was associated with being older, living in Toronto/Peel, being Asian, and having an underlying disease (Table 3).

The age-adjusted case-fatality rate was not significantly higher for patients infected with penicillin-nonsusceptible *S pneumoniae* than for those infected with penicillin-susceptible strains (Figure 1). Although mortality was elevated in patients infected with pneumococci that were highly resistant to penicillin and cefotaxime (MIC ≥4.0 μg/mL) compared with those infected with susceptible pneumococci, this difference was not statistically significant.

No statistically significant association was found between death and infection with penicillin- and cefotaxime-nonsusceptible pneumococci (Table 4). However, a statistically significant association was found between deaths after the fourth hospital day and infection with strains that had penicillin MICs of 4.0 μg/mL or higher or cefotaxime MICs of 2.0 μg/mL or higher. Not enough patients were infected with strains that had cefotaxime MICs of 4.0 μg/mL or higher to model this level of resistance separately.

By extrapolating our 1996 data to the entire US population, we estimated the number of cases of pneumococcal pneumonia in the United States. Our estimates were restricted to hospitalized patients. The number of patients with invasive pneumococcal pneumonias requiring hospitalization in 1996 was 31 479. One fifth to one third of pneumococcal pneumonias are bacteremic.[2,25] We assumed that 10% of the invasive pneumococcal infections were not detected by our surveillance system because the patients died before cultures could be obtained or because cultures were not done upon the patients' arrival at the hospital or were done after antibiotic administration, decreasing the yield of cultures. Incorporating these assumptions, the number of nonbacteremic pneumonias in 1996 was 71 000 to 140 000 and the total number of pneumococcal pneumonias was 106 000 to 175 000.

To calculate the number of deaths from pneumococcal pneumonia, we used our age-adjusted case-fatality rate of 12% for invasive cases. However, for nonbacteremic pneumococcal pneumonia, the case-fatality rate has been estimated to be one third to one half of that for bacteremic pneumonia.[2,6,25] Therefore, the estimated total number of deaths from pneumococcal pneumonia that required hospitalization in the United States in 1996 was 7000 to 12 500.

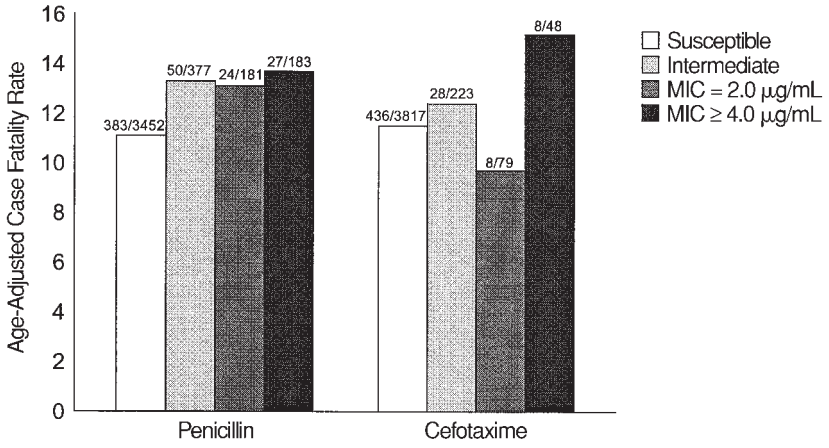
Discussion

Pneumococcal pneumonia has continued to cause significant mortality in the 1990s. In our analysis, the case-fatality rate of 12% among persons hospitalized with community-acquired, invasive pneumococcal pneumonia does not differ substantially from the rates reported over the last few decades.[2–7,10] Older age remains one of the strongest predictors of pneumococcal mortality. However, our data suggest that older patients cannot be considered as a homogeneous group with regard to mortality. The case-fatality rate among patients aged 65 to 75 years (13%)

TABLE 3—Results of Logistic Regression Analysis of the Association of Demographic Characteristics[a] With Mortality From Community-Acquired, Invasive Pneumococcal Pneumonia Requiring Hospitalization, 1995–1997

	n	Adjusted Odds Ratio (95% Confidence Interval)	*P*
Age, y			
≤17	155	Reference	. . .
18–64	1186	5.1 (1.2, 21.0)	.026
65–74	381	5.8 (1.4, 25.0)	.017
≥75	654	12 (2.8, 49.0)	<.001
Race			
Asian	72	1.9 (1.0, 3.5)	.042
Black	653	1.0 (0.7, 1.5)	.87
White	1421	Reference	. . .
Other/unknown	230	1.3 (0.8, 3.9)	.26
Geographic area[b]			
California	445	1.1 (0.7, 1.8)	.53
Connecticut	320	Reference	. . .
Maryland	788	0.70 (0.5, 1.1)	.11
Minnesota	138	0.56 (0.3, 1.2)	.15
Texas	146	0.81 (0.5, 1.5)	.49
Toronto/Peel	539	1.5 (1.0, 2.3)	.037
Underlying disease			
Absent	898	Reference	. . .
Present	1478	2.8 (2.0, 3.9)	<.001

[a]All characteristics shown were included in the model.
[b]Connecticut was considered the reference area because it had the median age-adjusted case-fatality rate. Georgia, Tennessee, and Oregon were excluded because they did not collect information on underlying disease. From other states, only cases in which information about underlying disease was available were included.



Note. Number of deaths over total number of patients at each level of susceptibility is listed above each bar. Case-fatality rates are age adjusted according to 3 age categories—0–17, 18–64, and >65 years of age. *P* > .05 for comparisons of case-fatality rates between all levels of nonsusceptible and susceptible pneumococci. MIC = minimum inhibitory concentration.

FIGURE 1—Association between penicillin and cefotaxime susceptibility level and case-fatality rate from community-acquired, invasive pneumococcal pneumonia requiring hospitalization, 1995–1997.

was more similar to that seen in younger age groups than that seen in older age groups. The presence of severe underlying disease is the other factor that consistently predicts mortality from invasive pneumococcal pneumonia.[6–8,10,12,25] Our data also support more recent observations that mortality from invasive pneumococcal pneumonia is not increased among patients with HIV infection without AIDS.[23,24]

Case-fatality rates also varied significantly by geographic location, with the lowest rate in Maryland and the highest in Toronto/Peel. These differences most likely reflect variability in hospitalization practices by region, which has been shown before.[26] Differences in mortality among hospitalized patients in Boston, Mass, and New Haven, Conn, have been ascribed to differences in hospital admission practices in the 2 cities rather than to any discrepancy in hospital care or overall mortality.[26] In addition, variation in blood culture collection practices by area may have contributed to the regional differences in case-fatality rates.

Although rates of invasive pneumococcal disease are higher for Blacks,[27] mortality was not increased in this group compared with Whites. The excess mortality seen among Asians has not been reported before. It is unclear whether it reflects biological, cultural, or medical practice differences.[28]

In our study, mortality from community-acquired, invasive pneumococcal pneumonia requiring hospitalization was not elevated in most infections due to β-lactam–resistant pneumococci. However, in a subset of patients who died after the first few days of illness, increased mortality was associated with infection with highly resistant pneumococci. Although case reports have shown worse clinical outcomes in patients with pneumococcal pneumonia caused by β-lactam–nonsusceptible organisms,[29–31] this observation has not been confirmed by studies that control for potential confounding factors.

In 2 previous studies of bacteremic pneumococcal pneumonia, no difference in mortality was found between those with susceptible and those with nonsusceptible pneumococci when age, underlying disease, and severity of illness on presentation were controlled for.[32,33] In these analyses, however, the few patients infected with pneumococci who had penicillin MICs of 4.0 μg/mL or higher were not evaluated independently. Our data showed no increased mortality among patients infected with pneumococci who had penicillin MICs of 0.12 to 2.0 μg/mL compared with those infected with susceptible strains, but patients infected with pneumococci who had penicillin MICs of 4.0 μg/mL or higher had more than 7 times the risk of death after the fourth hospital day (Table 4). We found no excess mortality among patients infected with cefotaxime-intermediate strains. Our model did show a significant association between late deaths and a cefotaxime MIC of 2.0 μg/mL or higher; however, only 16 patients with 2 deaths were included in this category.

TABLE 4—Results of Logistic Regression Analysis[a] of the Association Between Penicillin and Cefotaxime Nonsusceptibility and Mortality From Community-Acquired, Invasive Pneumococcal Pneumonia Requiring Hospitalization, 1995–1997

Level of Antibiotic Susceptibility	All Deaths Included[b]		Deaths After the Second Hospital Day[c]		Deaths After the Fourth Hospital Day[d]	
	n[e]	OR (95% CI)	n[e]	OR (95% CI)	n[e]	OR (95% CI)
Penicillin MIC, μg/mL						
≥4.0	20	2.3 (0.7, 7.4)	19	5.5 (1.3, 23.0)	19	7.1 (1.7, 30.0)
2.0	37	1.3 (0.5, 3.7)	33	0.50 (0.06, 4.2)	33	0.65 (0.08, 5.5)
0.12–1.0	92	1.4 (0.8, 2.6)	84	1.3 (0.6, 3.2)	81	1.0 (0.3, 3.0)
<0.12	1095	Reference	1037	Reference	1018	Reference
Cefotaxime MIC, μg/mL						
≥2.0	16	1.3 (0.3, 5.9)	16	4.3 (0.8, 24.0)	16	5.9 (1.1, 33.0)
1.0	35	1.4 (0.5, 3.9)	32	1.2 (0.2, 5.6)	32	1.5 (0.3, 7.4)
<1.0	1173	Reference	1107	Reference	1086	Reference

Note. OR = Odds ratio; CI = confidence interval; MIC = minimum inhibitory concentration.
[a]Separate models were used for penicillin and cefotaxime; each model controlled for age, race, geographic location, and underlying disease status. Patients with missing data for any of the variables in the model were excluded. Only data from Maryland, California, Toronto, and Texas are included in the models because only in these areas were complete data available on both underlying disease status and antibiotic MICs.
[b]N = 1244, deaths = 147. There were 12 more cases in the penicillin model because samples from 12 patients were tested for penicillin susceptibility but not cefotaxime susceptibility.
[c]N = 1173, deaths = 76.
[d]N = 1151, deaths = 54.
[e]Number of patients at each level of susceptibility decreases in subsequent models because of deaths during the first few hospital days.

The discrepancy between the effects of β-lactam resistance on pneumococcal pneumonia and meningitis is supported by pharmacodynamic data. The effectiveness of β-lactam antibiotics is correlated with the duration of local antibiotic concentration above the MIC of the infecting organism.[34,35] Antibiotic concentrations in the cerebrospinal fluid and middle ear fluid are lower than concentrations seen simultaneously in the serum.[36,37] The clinical consequences of this finding are reflected by reports of treatment failures in cases of meningitis[15–17] and otitis media[38,39] caused by nonsusceptible pneumococci.

In contrast, drug concentrations in the lung interstitia are much more similar to those found in serum.[36] The serum concentrations of parenteral β-lactam antibiotics have been shown to have adequate time above the MIC of intermediate and most resistant pneumococci to effect successful bacteriologic killing.[34,36] However, as the MICs of resistant pneumococci rise, the pharmacodynamic parameters of standard doses of β-lactam antibiotics may reach a point at which the duration above the MIC falls below the critical threshold.[40] Our data suggest that this point may be at or near a penicillin MIC of 4.0 μg/mL, but further studies are needed to corroborate this finding.

Another important observation in our study was that the effect of higher levels of β-lactam resistance on mortality became significant only when deaths within the first few hospital days were excluded. Austrian and Gold[6] pointed out more than 3 decades ago that the dramatic reduction in pneumococcal pneumonia mortality attributable to penicillin was evident only after the fifth day of illness. Mortality early in the course probably reflects factors other than therapeutic interventions, such as the severity of the presenting illness. Therefore, any association between β-lactam resistance and increased mortality would become more evident when fatalities during the first few days of illness were excluded, as shown in our study.

Use of surveillance data to evaluate the effect of antibiotic resistance on mortality has potential limitations. First, no data on the severity of illness on presentation were available. The increase in mortality seen in patients infected with pneumococci with higher MICs may reflect more severe presentations. Severity of presentation has not been directly linked to infection with resistant pneumococci but is related to underlying disease.[29,30,41] Underlying disease is often associated with resistance caused by recent antibiotic use. Although we adjusted for underlying disease in our model, some residual confounding may have occurred.

Second, we were unable to serotype most pneumococcal isolates. Despite a few older studies that found increased mortality in serotype 3 infections,[2,6] virulence has not been consistently linked to other serotypes. Resistance to penicillin has been shown to be uncommon in serotype 3 pneumococci but is most common in several other serotypes (6B, 9V, 14, 19A, 23F).[42] In our study, the 10 fatal cases of infection with pneumococci with penicillin MICs of 4.0 μg/mL or higher involved common resistant serotypes (3 each of 9V, 14, and 23F; 1 of 6B).

Third, we did not have information available on antibiotic treatment. Thus, we could not ascribe the increase in late mortality among patients infected with highly resistant pneumococci to treatment failure. Penicillin-resistant pneumococci are often resistant to other classes of antibiotics recommended for community-acquired pneumonia.[43] In our surveillance data, 55% of the pneumococci with penicillin MICs of 4.0 or higher were resistant to cefotaxime, and 53% were resistant to erythromycin; these findings were consistent with those of other studies.[44,45] Although we did not perform MIC testing of second-generation cephalosporins in this study, these agents have MIC profiles more similar to that of penicillin than to those of third-generation cephalosporins.[46] Future studies of antibiotic-resistant pneumococcal pneumonia need to define better the particulars of antibiotic administration so that treatment failure can be further evaluated in the setting of elevated MICs.

Our results indicate an estimated 7000 to 12 500 deaths among persons hospitalized with pneumococcal pneumonia in the United States in 1996. Our study was the first to use population-based surveillance data to project the annual number of deaths from pneumococcal pneumonia in the United States. Two previous estimates of 40 000 annual deaths from pneumococcal pneumonia used other methods of approximation.[3,47,48] The previ-

ous figure may be an overestimate, but the lower estimate in our study may be explained partially by recent increases in the use of pneumococcal polysaccharide vaccine and increases in out-of-hospital mortality[49,50] (National Center for Health Statistics, unpublished data, 1998). In addition, because our projections were based on invasive pneumococcal infections, we adjusted for bacteremias missed because of inadequate or lack of blood cultures; however, our 10% adjustment may have underestimated missed bacteremias.

Many people still die each year in the United States from pneumococcal pneumonia. However, our study corroborates earlier findings that the recent appearance of widespread antibiotic resistance in pneumococci has not led to substantial increases in pneumonia mortality. The National Committee for Clinical Laboratory Standards breakpoints for penicillin- and cefotaxime-intermediate and -resistant pneumococci, which were based on meningitis treatment failures, may be inappropriate for pneumococcal pneumonia. Further research is needed to better elucidate the critical threshold of antibiotic resistance for pneumonia treatment. In addition, future studies of clinical treatment failures should focus on mortality after the first few days of illness.

The proportion of pneumococcal pneumonia patients infected with highly resistant strains is still small but is increasing in the United States. In 1995, 3.9% of pneumococci in our surveillance system had a penicillin MIC of 4.0 μg/mL or higher. This percentage increased to 5.5% and 7.8% in 1996 and 1997, respectively. Nonetheless, factors other than resistance, such as older age and underlying disease, continue to be the most important influences on mortality in the era of antibiotic resistance. As the US population ages, increased use of the polysaccharide pneumococcal vaccine in these high-risk groups is essential to reduce mortality from invasive pneumococcal disease.[22,49] □

Contributors

All authors contributed to the study design and writing of the paper. D. R. Feikin did the primary analysis and wrote the paper. A. Schuchat established the surveillance system and planned the analysis. M. Kolczak assisted in statistical analysis. N. L. Barrett coordinated the study in Connecticut. L. H. Harrison coordinated the study in Maryland. L. Lefkowitz coordinated the study in Tennessee. A. McGeer coordinated the study in Toronto, Ontario. M. M. Farley coordinated the study in Georgia. D. J. Vugia coordinated the study in California. C. Lexau coordinated the study in Minnesota. K. R. Stefonek coordinated the study in Oregon. J. E. Patterson coordinated the study in Texas. J. H. Jorgensen did the antibiotic susceptibility testing.

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