
Opportunities for Prevention in the Conjugate Vaccine Era

Katherine A. Robinson, MPH
Wendy Baughman, MSPH
Gretchen Rothrock, MPH
Nancy L. Barrett, MS, MPH
Margaret Pass, MS, CIC
Catherine Lexau, MPH
Barbara Damaske
Karen Stefonek, MPH
Brenda Barnes, RN
Jan Patterson, MD
Elizabeth R. Zell, MStat
Anne Schuchat, MD
Cynthia G. Whitney, MD, MPH

for the Active Bacterial Core Surveillance (ABCs)/Emerging Infections Program Network

**Context** Pneumococcal polysaccharide vaccine is recommended for elderly persons and adults with certain chronic illnesses. Additionally, a recently licensed pneumococcal 7-valent conjugate vaccine has been recommended for use in young children and could dramatically change the epidemiology of pneumococcal disease.

**Objectives** To assess pneumococcal disease burden in the United States, estimate the potential impact of new vaccines, and identify gaps in vaccine recommendations.

**Design and Setting** Analysis of data from the Active Bacterial Core Surveillance (ABCs)/Emerging Infections Program Network, an active, population-based system in 9 states.

**Patients** A total of 15860 cases of invasive pneumococcal disease occurring between January 1, 1995, and December 31, 1998.

**Main Outcome Measures** Age- and race-specific pneumococcal disease incidence rates per 100000 persons, case-fatality rates, and vaccine preventability.

**Results** In 1998, overall incidence was 23.2 cases per 100000, corresponding to an estimated 62840 cases in the United States. Incidence was highest among children younger than 2 years (166.9) and adults aged 65 years or older (59.7). Incidence among blacks was 2.6 times higher than among whites (95% confidence interval [CI], 2.4-2.8). Overall, 28.6% of case-patients were at least 65 years old and 85.9% of cases in this age group were due to serotypes included in the 23-valent polysaccharide vaccine; 19.3% of case-patients were younger than 2 years and 82.2% of cases in this age group were due to serotypes included in the 7-valent conjugate vaccine. Among patients aged 2 to 64 years, 50.6% had a vaccine indication as defined by the Advisory Committee on Immunization Practices (ACIP). The case-fatality rate among patients aged 18 to 64 years with an ACIP indication was 12.1% compared with 5.4% for those without an indication (relative risk, 2.2; 95% CI, 1.7-2.9).

**Conclusions** Young children, elderly persons, and black persons of all ages are disproportionately affected by invasive pneumococcal disease. Current ACIP recommendations do not address a subset of persons aged 18 to 64 years but do include those at highest risk for death from invasive pneumococcal disease.

**JAMA.** 2001;285:1729-1735
ministered along with routine infant immunizations.\textsuperscript{10} This vaccine may change the epidemiology of pneumococcal disease dramatically in the next decade. We used the Active Bacterial Core Surveillance (ABCs)/Emerging Infections Program Network, a multistate surveillance project, to investigate the burden of invasive disease caused by \textit{S pneumoniae} in 1995-1998. We sought to estimate the expected effect of the recently licensed vaccine for infants and children and to identify remaining gaps in disease prevention in all age groups.

### METHODS

Cases of invasive disease due to \textit{S pneumoniae} were identified through the ABCs/Emerging Infections Program Network from January 1, 1995, through December 31, 1998. Active Bacterial Core Surveillance conducted active, laboratory-based surveillance in 9 areas: the San Francisco Bay area, California (3 counties, start date: January 1, 1995, end date: October 21, 1995; 1 county, start date: October 22, 1995), the state of Connecticut (start date: March 1, 1995), Atlanta, Ga (8 counties, start date: January 1, 1995; 20 counties, start date: January 1, 1997), Baltimore, Md (6 counties, start date: January 1, 1995), Minneapolis–St Paul, Minn (7 counties, start date: April 1, 1995), Rochester, NY (7 counties, start date: July 1, 1997), Portland, Ore (3 counties, start date: July 1, 1995), urban areas within Tennessee (5 counties, start date: January 1, 1995), and San Antonio, Tex (1 county, start date: January 1, 1995, end date: September 30, 1996). The aggregate population in 1998 for the 8 areas that participated was 17.4 million, or 6.4% of the US population.

Active Bacterial Core Surveillance methods have been published previously.\textsuperscript{2,5,11-13} Invasive pneumococcal disease was defined as isolation of \textit{S pneumoniae} from a normally sterile site (eg, blood, cerebrospinal fluid) in a resident of 1 of the surveillance areas. To identify cases in each surveillance area, project personnel communicated regularly with contacts in all participating clinical microbiology laboratories in the defined geographic areas. In 1998, 385 (98%) of 391 laboratories in the surveillance area participated. We verified the completeness of case ascertainment every 6 months through laboratory audits, during which surveillance personnel reviewed records of all clinical laboratories. Surveillance personnel or infection control practitioners reviewed medical charts and completed standardized case-report forms with information on demographic characteristics, clinical syndromes, underlying conditions, and outcomes of illness. In 1995-1996, the presence of 1 or more underlying conditions that are considered indications for vaccination by the Advisory Committee on Immunization Practices (ACIP)\textsuperscript{4} (ie, chronic cardiovascular diseases, chronic pulmonary diseases, chronic liver diseases, diabetes, alcohol abuse, asplenia, immunosuppressive conditions, organ or bone marrow transplant, chronic renal failure or nephrotic syndrome, and cerebrospinal fluid leakage) was systematically recorded for all pneumococcal cases in Maryland and Texas; in 1997, underlying disease information was recorded in Maryland, Connecticut, and California. Information on underlying disease was collected for all cases in counties within 7 states with an aggregate population of approximately 14 million during 1998. Underlying disease data were systematically collected for all invasive cases within the participating geographic areas, rather than in a biased fashion. Case-patients who died during hospitalization or an episode of illness related to pneumococcus were counted as deaths for case-fatality rates.

Available isolates were collected from identified cases and isolates from 1998 were sent to the Centers for Disease Control and Prevention (CDC), Atlanta, Ga; the University of Texas Health Science Center at San Antonio; or the Minnesota Department of Health, Minneapolis, where identification was confirmed by susceptibility to optochin and bile solubility. Serotyping was performed at the CDC or the Minnesota Department of Health with type-specific antisera (Quellung reaction).

Analysis was based on the serotypes included in the 7-valent conjugate vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F), the 9-valent conjugate vaccine (those in the 7-valent conjugate vaccine and serotypes 1 and 5), the 11-valent conjugate vaccine (those in the 9-valent conjugate vaccine and serotypes 3 and 7F), and the 23-valent polysaccharide vaccine (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F). We considered serotypes to be potentially cross-reactive if they were in the same serogroup as a vaccine type (eg, 6A).

We considered cases to be meningitis if the pathogen was isolated from cerebrospinal fluid or if the pathogen was isolated from blood and a clinical diagnosis of meningitis was recorded in the patient’s medical record. Cases were considered to have bacteremia without focus if the pathogen was isolated only in the blood and no syndrome other than bacteremia or sepsis was reported. Recurrent pneumococcal disease was defined as occurring if a second positive culture from the same case-patient was obtained at least 8 days after the initial culture was collected.

Incidence rates of invasive pneumococcal disease were calculated using data from areas with a full calendar year of surveillance and US Bureau of the Census postcensal population estimates. All other analyses used all data available, including data collected during partial years of surveillance. For national projections of cases and comparisons between sites, we applied age- and race-specific rates of disease from the surveillance areas to the age and racial distribution of the US population for the corresponding year. For these projections, case-patients with unknown race were distributed based on reported local race distribution of patients within 8 age categories.

Analysis was performed using SAS, version 6.12 (SAS Institute Inc, Cary, NC), and EpiInfo, version 6.04c (CDC).
RESULTS

Descriptive Epidemiology

From 1995 to 1998, 15,860 cases of invasive pneumococcal disease were reported to ABCs. Case-patients ranged in age from 0 days to 104 years (median, 43 years). Thirty-six percent (5,247/14,430) of all cases with known race were black, and 55% of case-patients were male. While 78% of all patients were hospitalized, only 38% of children younger than 18 years were hospitalized vs 92% of adults aged 18 to 64 years and 96% of adults aged at least 65 years. Most cases were diagnosed as pneumonia (n=8,837; 52.7%) or bacteremia without focus (n=6,395; 40.3%); 709 case-patients had meningitis (4.5%). Since 1995, 425 patients (3%) had more than 1 episode of invasive pneumococcal disease reported; the number of recurrences ranged from 1 to 5.

Disease Burden

Incidence. In 1998, the overall incidence of invasive disease was 23.2 per 100,000 (TABLE 1). Incidence was highest among children younger than 2 years (166.9), with rates in the second year of life exceeding rates in the first year (184.2 vs 150.5). Rates were lowest among those aged 5 to 17 years (3.9) and increased with increasing age to 54.0 among adults aged at least 65 years. An estimated 33,100 cases (53%) in the United States in 1998 occurred among children younger than 2 years and adults aged 65 years and older (TABLE 2). The overall rate among blacks was 49.7 compared with 19.7 for whites (relative risk [RR], 2.6; 95% confidence interval [CI], 2.4-2.8). The RR of invasive disease among blacks compared with whites was higher in every age category (FIGURE), with the greatest racial disparity in the age range of 35 to 49 years (blacks, 58.1 per 100,000; whites, 10.3 per 100,000; RR, 5.6; 95% CI, 4.9-6.5).

Standardized rates of pneumococcal disease ranged from 17.8 cases per 100,000 in Tennessee in 1995 to 42.5 in California in 1995. The rate in California decreased 22% from 42.5 to 33.1 during the 4-year period, primarily because of a decline in incidence among men aged 18 to 64 years. There were no significant temporal trends in disease rates in the other surveillance areas.

During 1998, the age-specific disease rates differed by geographic area (TABLE 1). Among patients younger than 2 years, the disease rate in Minnesota (274.0 per 100,000) was 2.4 times higher than in Maryland (113.1). Among case-patients aged 18 to 34 years, the rate was 4.9 to 7.1 in all sites except Maryland (9.3) and California (14.0). In California, the rate among case-patients aged 35 to 49 years (45.8) was 2.5 to 3.4 times higher than in the other areas (range, 13.6-18.5), and, among case-patients aged 50 to 64 years, the rate in California (45.1) was 1.8 to 2.6 times higher than in other areas (range, 17.3-24.8). The disease rate among persons aged at least 80 years varied from 76.1 in California to 123.9 in Georgia.

Deaths. The case-fatality rate was 10.0% for all reported cases (1,556 deaths/15,544 cases). Case-fatality rates increased from 1.4% among persons younger than 2 years to 20.6% among persons aged 80 years or older (FIGURE). Death was more common among persons with pneumococcal meningitis (16.7%) compared with all other syndromes combined (9.8%) (RR, 1.7; 95% CI, 1.4-2.0; P<.001). Case-fatality rates were higher for pneumococcal meningitis than for pneumonia or bacteremia in all age categories, with the greatest differences in persons aged 18 to 49 years (22.1% vs 7.8% and 10.9%, respectively) and those aged at least 80 years (50% vs 20.3% and 20.3%, respectively).

The mortality rate was highest among elderly persons (for those aged 65-79 years, 7.4 deaths per 100,000; for those aged ≥80 years, 17.4). Persons aged 65 years or older accounted for 51.4% of

©2001 American Medical Association. All rights reserved.

(Reprinted) JAMA, April 4, 2001—Vol 285, No. 13 1731
all deaths due to invasive pneumococcal disease in 1998 (Table 2). The age-specific case-fatality rates for blacks and whites did not differ significantly. The mortality rate for blacks was higher compared with whites in every age category except 2- to 4-year-olds (no deaths in either group) and 5 to 17 years (0 deaths among blacks and 3 deaths among whites). For other age groups, the difference in mortality was accounted for by the difference in disease incidence.

Of 2869 case-patients aged 18 to 64 years who were assessed for underlying disease, 1683 (59%) had 1 or more underlying conditions designated as ACIP indications for vaccination. The case-fatality rate was 12.1% for patients with these conditions compared with 5.4% among patients aged 18 to 64 years without these conditions (RR, 2.2; 95% CI, 1.7-2.9; P < .001). Case-fatality rates were highest for those with congestive heart failure (27%), nonhematologic malignancy (22%), and renal failure requiring dialysis (20%) (Table 3). Among persons aged 18 to 49 years with invasive pneumococcal disease, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) was the most common underlying condition reported overall and the second most common underlying condition for those who died of pneumococcal disease in that age group. Although case-fatality was low among children aged 2 to 17 years, it was higher among children with an ACIP vaccine indication (3/73; 4%) than among other children (5/528; 0.9%).

Vaccine-Preventable Cases. Of all pneumococcal cases identified, 28.6% (n = 4529) were in persons aged at least 65 years. Of 3469 case-patients aged 2 to 64 years for whom underlying conditions were assessed, 50.6% (n = 1755) had 1 or more underlying conditions designated as ACIP indications for vaccination.
had at least 1 condition that was a known ACIP indication for pneumococcal polysaccharide or conjugate vaccine. A total of 19.3% of cases (n = 3064) were in persons younger than 2 years, a target group for conjugate vaccines. Based on 1998 projections, 48000 cases (76%) of invasive pneumococcal disease and 5300 pneumococcal deaths (87%) occurred in 1 year in the United States in persons who were eligible for pneumococcal vaccines.

Isolates were serotyped for 3610 cases (86.2%) reported in 1998 (TABLE 4). Serotypes included in the 7-valent conjugate vaccine accounted for 82.2% of strains among children younger than 2 years, 82.7% among children aged 2 to 4 years, 53.1% among adults aged 50 to 64 years, and 56.2% among adults aged at least 65 years. Serotypes potentially cross-protected by the 7-valent vaccine accounted for an additional 10.2% and 11.6% among children younger than 2 years and adults aged at least 65 years, respectively. Serotypes in an 11-valent conjugate vaccine formulation provided little additional protection for children but accounted for 65.3% of strains in adults aged at least 65 years, with an additional 11.7% of strains potentially covered by cross-protection. Serotypes in the 23-valent vaccine accounted for 85.9% of strains from adults aged at least 65 years; 8.3% were potentially cross-protected.

**COMMENT**

Based on active case finding in a multistate population of more than 17 million, invasive infection with *S pneumoniae* was estimated to cause more than 62000 cases and more than 6000 deaths in the United States in 1998. More than half of these cases occurred in adults who had an indication for pneumococcal polysaccharide vaccination, including persons aged at least 65 years and persons aged 18 to 64 years with chronic illnesses that are vaccine indications. Another 20% of cases occurred in children younger than 2 years, a group for whom vaccination has recently been recommended.

Consistent with previous studies, the highest rates of disease occurred among children, particularly those younger than 2 years. Analysis of isolates from children younger than 2 years suggests that at least 82% of disease was caused by serotypes included in the 7-valent pneumococcal conjugate vaccine. Because efficacy of this vaccine against invasive disease was more than 90% in a prelicensure trial, major changes in the epidemiology of invasive pneumococcal disease, including disease due to antibiotic-resistant strains, among children are anticipated following widespread use of this vaccine. Although no increase in disease due to nonvaccine serotypes occurred in the prelicensure trial, it is too soon to tell whether disease due to other serotypes will increase following widespread use.

After age 5 years, the risk of invasive pneumococcal disease increases with increasing age. Elderly persons have the highest risk of death due to invasive pneumococcal disease; persons aged at least 65 years account for 56% of all deaths but only 28.6% of cases. The 23-valent pneumococcal polysaccharide vaccine has demonstrated effectiveness against bacteremic pneumococcal disease and has been shown to be cost-effective for persons aged at least 65 years.

**TABLE 4. Most Common Serotypes Among Pneumococcal Disease Case-Patients, 1998**

<table>
<thead>
<tr>
<th>Pneumococcal Case-Patients, %*</th>
<th>All Ages (n = 3610)</th>
<th>&lt;2 y (n = 735)</th>
<th>2-64 y (n = 1844)</th>
<th>≥65 y (n = 1031)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Individual serotypes†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>17.6</td>
<td>33.5</td>
<td>12.5</td>
<td>15.2</td>
</tr>
<tr>
<td>4</td>
<td>10.5</td>
<td>7.8</td>
<td>12.4</td>
<td>9.1</td>
</tr>
<tr>
<td>9V</td>
<td>8.5</td>
<td>5.2</td>
<td>9.4</td>
<td>9.2</td>
</tr>
<tr>
<td>6B</td>
<td>7.7</td>
<td>10.6</td>
<td>6.6</td>
<td>7.8</td>
</tr>
<tr>
<td>23F</td>
<td>7.4</td>
<td>7.2</td>
<td>6.9</td>
<td>8.4</td>
</tr>
<tr>
<td>19F</td>
<td>5.5</td>
<td>10.2</td>
<td>4.4</td>
<td>4.1</td>
</tr>
<tr>
<td>18C</td>
<td>4.8</td>
<td>7.8</td>
<td>5.0</td>
<td>2.3</td>
</tr>
<tr>
<td>6A</td>
<td>4.3</td>
<td>4.6</td>
<td>3.8</td>
<td>4.8</td>
</tr>
<tr>
<td>12F</td>
<td>3.8</td>
<td>1.4</td>
<td>4.8</td>
<td>3.6</td>
</tr>
<tr>
<td>3</td>
<td>3.3</td>
<td>0.4</td>
<td>3.4</td>
<td>5.0</td>
</tr>
<tr>
<td>19A</td>
<td>3.3</td>
<td>3.5</td>
<td>3.0</td>
<td>3.5</td>
</tr>
<tr>
<td>22F</td>
<td>3.2</td>
<td>0.4</td>
<td>3.2</td>
<td>5.3</td>
</tr>
<tr>
<td>7F</td>
<td>2.8</td>
<td>0.5</td>
<td>4.0</td>
<td>2.2</td>
</tr>
<tr>
<td>1</td>
<td>2.4</td>
<td>0.4</td>
<td>3.6</td>
<td>1.7</td>
</tr>
<tr>
<td>All others</td>
<td>15.0</td>
<td>6.5</td>
<td>16.9</td>
<td>17.6</td>
</tr>
<tr>
<td><strong>Serotypes included in vaccines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-Valent</td>
<td>62.0</td>
<td>82.2</td>
<td>57.2</td>
<td>56.2</td>
</tr>
<tr>
<td>9-Valent</td>
<td>64.5</td>
<td>82.6</td>
<td>61.0</td>
<td>58.0</td>
</tr>
<tr>
<td>11-Valent</td>
<td>70.6</td>
<td>83.5</td>
<td>68.4</td>
<td>65.3</td>
</tr>
<tr>
<td>23-Valent</td>
<td>88.1</td>
<td>$</td>
<td>88.2</td>
<td>85.9</td>
</tr>
</tbody>
</table>

*Percentages may not sum to 100.0% because of rounding.
†All serotypes accounting for at least 2% of all cases are listed individually.
‡23-Valent polysaccharide vaccine is not recommended for children younger than 2 years.
is routinely recommended. Based on analysis of cases for which data on underlying disease were collected, 59% of disease in persons aged 18 to 64 years occurred in persons with an indication for vaccine. Coverage among persons with ACIP indications in this age group has been much lower than coverage among older persons; increased use of the polysaccharide vaccine in this age group would result in significant disease reductions.

Some reductions also may be possible through expanding use of highly active antiretroviral therapy among patients with HIV infection. A 22% reduction in invasive pneumococcal disease was observed in San Francisco, Calif, between 1995 and 1998 and was likely due to immune reconstitution in HIV patients through highly active antiretroviral therapy. Introduction of conjugate vaccine for young children could lead to some disease reductions in adults through decreased transmission, since exposure to children has been shown to be a risk factor for adult disease.

We identified substantial geographic variation in the age- and race-adjusted incidence of pneumococcal disease. These differences are likely multifactorial and may be explained by regional differences in diagnostic routines, such as blood culture collection, and differences in individual or community risk factors, such as prevalence of HIV/AIDS and of persons living in poverty. We found marked disparity in disease incidence between blacks and whites in every age group. Several reports have highlighted the higher incidence of invasive pneumococcal disease among American Indians (ie, Navajo and White Mountain Apaches), Alaska natives, and blacks. A case-control study of nonelderly adults who were not immunocompromised found that the risk associated with black race persisted despite adjustment for multiple other factors. However, a similar study of population-based risk factors for invasive pneumococcal disease in children younger than 5 years found no racial differences independently associated with invasive pneumococcal disease.

Higher prevalence of certain underlying diseases (eg, diabetes, HIV infection) among blacks may contribute to the observed increased rates in our sample. Also, blacks are much less likely to have received the 23-valent polysaccharide vaccine than are whites. Despite the lack of full explanation for racial gaps in disease occurrence, real opportunity for eliminating disparity exists. Use of pneumococcal conjugate vaccines in young children has the potential to eliminate the black-white gap in disease incidence, as has previously been achieved through the widespread use of Haemophilus influenzae type b conjugate vaccine.

Our report reflects the experience of active surveillance over 4 years in a population comprising more than 6% of the United States. Nevertheless, certain limitations bear mentioning. First, we were unable to determine ethnicity for many patients and had limited numbers of patients among Asians and Native Americans; these factors restricted the estimates we could make for Hispanic ethnicity and race other than white or black. Next, the case definition required isolation of S.pneumoniae from a normally sterile site; failure to collect blood cultures or collection of cultures after antibiotic therapy began may have led to underestimation of the disease incidence. Our estimates of disease burden do not include noninvasive disease; therefore, our estimates may differ from previous disease estimates. Presence of underlying conditions was not validated and vaccination status was not available. Consequently, we were unable to determine whether disease may have been due to lack of vaccination or to vaccine failure. Our estimates of preventability, therefore, do not take into account the number of times the vaccine failed to work.

The availability of new vaccines for prevention of pneumococcal disease in young children represents the culmination of decades of groundwork; the next decade offers a challenge to ensure that the major prevention opportunities these tools promise are realized. Continued surveillance will help determine if replacement disease occurs and if population immunity is conferred by vaccinating millions of young children. The aging of the US population and the major burden of pneumococcal illness and death among adults and elderly persons provide additional challenges: improving utilization of the best tool currently available—the 23-valent polysaccharide vaccine—and promoting research and development of improved pneumococcal vaccines. Goals for better adult vaccines should include prevention of pneumonia, higher efficacy in immunocompromised populations, and confluence of long-term protection.
Members of the ABCs/Emerging Infections Program Network: Lilian Billmann, RN, Yvonne Deane-Hibbert, Kim Holmes, MS, CIC, Lee Harrison, MD, and Jackie Hunter, Maryland Emerging Infections Program; Lisa Gelling, MPH, Art Reingold, MD, and Duc Vu gia, MD, MPH, California Emerging Infections Program; Maureen Cassidy, Paul Cieslak, MD, and Jane Donegan, RN, Oregon Emerging Infections Program; Renee Belnichard, John Besser, Susan Johnson, Ruth Lynfield, MD, Jean Rainbow, MPH, Brenda Sayler, Lori Triden, and Karen White, MPH, Minnesota Emerging Infections Program; Sabrina Burden, MPH, Shama Desai, MPH, Monica Farley, MD, Patricia Martell-Cleary, MPH, and Suzanne Segler, MPH, Georgia Emerging Infections Program; Allen Craig, MD, Lewis Leffkowitz, MD, and Bill Schaffner, MD, Tennessee Emerging Infections Program; Nancy Bennett, MD, Bruce Hatheway, Dale Morse, MD, and Perry Smith, MD, New York Emerging Infections Program; Craig Morin, MPH, and James Hadler, MD, Connecticut Emerging Infections Program; Denise Miller and James Jorgen sen, PhD, University of Texas Health Sciences Center at San Antonio, and Richard Facklam, PhD, LakeShonda Shealey, John Wolls, and Carolyn Wright, CDC.

Funding/Support: Financial support for this project was provided by the CDC’s Emerging Infections Program Network.

REFERENCES


