Changing Epidemiology of Invasive Pneumococcal Disease Among Older Adults in the Era of Pediatric Pneumococcal Conjugate Vaccine

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Context A conjugate vaccine targeting 7 pneumococcal serotypes was licensed for young children in 2000. In contrast to the 23-valent polysaccharide vaccine used in adults, the 7-valent conjugate vaccine affects pneumococcal carriage and transmission. Early after its introduction, incidence of invasive pneumococcal disease declined among older adults, a group at high risk for pneumococcal disease.

Objective To determine among adults aged 50 years or older whether incidence of invasive pneumococcal disease, disease characteristics, or the spectrum of patients acquiring these illnesses have changed over the 4 years since pneumococcal conjugate vaccine licensure.


Main Outcome Measures Incidence of invasive pneumococcal disease by pneumococcal serotype and other characteristics; frequency among case patients of comorbid conditions and other factors influencing mortality.

Results Incidence of invasive pneumococcal disease among adults aged 50 years or older declined 28% (95% confidence interval [CI], −31% to −24%), from 40.8 cases/100,000 in 1998-1999 to 29.4 in 2002-2003. Among those aged 65 years or older, the 2002-2003 rate (41.7 cases/100,000) was lower than the Healthy People 2010 goal (42 cases/100,000). Among adults aged 50 years or older, incidence of disease caused by the 7 conjugate vaccine serotypes declined 55% (95% CI, −58% to −51%) from 22.4 to 10.2 cases/100,000. In contrast, disease caused by any of the 16 serotypes only in polysaccharide vaccine did not change, and disease caused by serotypes not in either vaccine increased somewhat, from 6.0 to 6.8 cases/100,000 (13%; 95% CI, 1% to 27%). Between 1998-1999 and 2002-2003, the proportion of case-patients with human immunodeficiency virus infection increased from 1.7% (47/2,737) to 5.6% (124/2,231) (P<.001), and those with any comorbid condition that is an indication for pneumococcal polysaccharide vaccination increased from 62.3% (1,842/2,955) to 72.0% (1,721/2,390) (P<.001).

Conclusions Our findings indicate that use of conjugate vaccine in children has substantially benefited older adults. However, persons with certain comorbid conditions may benefit less than healthier persons from the indirect effects of the new vaccine.

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serotypes included in the vaccine.1–3 Because of this effect on pneumococcal carriage, especially in the age group most likely to be colonized (those <2 years),4 use of PCV-7 in children can affect pneumococcal transmission in the community.

Pneumococcal disease causes substantial morbidity and mortality among older adults. Consistent with PCV-7's ability to interrupt transmission, declines in invasive pneumococcal disease incidence among older adults were observed in 2001, the year after PCV-7 introduction.3 Our purpose was to closely examine disease in older adults in the conjugate vaccine era. We examined whether the observed early decline has continued over a longer period, whether disease characteristics have changed, and whether the spectrum of patients acquiring invasive pneumococcal disease has changed. Active Bacterial Core Surveillance (ABCs), a component of the Centers for Disease Control and Prevention (CDC) Emerging Infections Program, conducted surveillance for invasive pneumococcal disease continuously from 1998-2003, in defined populations in 8 states. Using ABCs data from the 2 years before PCV-7 licensure (1998-1999) and the 4 subsequent years, we evaluated the incidence of all invasive disease, of disease caused by specific pneumococcal serotypes, and of common disease syndromes. The proportions of case-patients with preexisting comorbid conditions and factors associated with death following invasive pneumococcal disease were also examined.

METHODS

Invasive pneumococcal disease was monitored prospectively in 8 surveillance areas: San Francisco County, California; the state of Connecticut; Atlanta, Ga (20-county metropolitan area); Baltimore, Md (6-county metropolitan area); Minneapolis-St Paul, Minn (7-county metropolitan area); Rochester, NY (7-county metropolitan area); Portland, Ore (3-county metropolitan area); and the Memphis, Nashville, Knoxville, and Chattanooga metropolitan areas in Tennessee (5 counties). In 2002, the estimated combined population in these areas was 18,813,000, with 4,978,000 persons aged 50 years or older. This report includes cases among persons aged 50 years or older, who are the focus of the analysis; incidence of invasive pneumococcal disease among children younger than 5 years is reported briefly for comparison. The protocol was presented to the institutional review boards at the CDC and the participating state health departments and academic centers. The protocol was determined to be exempt from requiring review at the CDC and some state health departments’ boards and was reviewed and approved by others.

As described previously,6 residents of surveillance areas were included as cases when pneumococcus was isolated from normally sterile sites, such as blood or cerebrospinal fluid. Hospital and reference laboratory records were audited periodically to ensure complete case reporting. Surveillance staff or infection control practitioners reviewed medical records and completed case reports. We defined a patient as having meningitis when pneumococcus was isolated from cerebrospinal fluid or when meningitis was diagnosed clinically and pneumococcus was isolated from another sterile site. We defined a patient as having invasive pneumonia when pneumococcus was isolated from pleural fluid or when pneumonia was diagnosed clinically and pneumococcus was isolated from blood or another sterile site. Cases of bacteremia without focus included those with blood isolates but no identified focus of infection. Data concerning the presence of certain comorbid conditions were collected in all reporting sites from 1998-2003, except for Georgia (2000-2003 only); in New York, information on human immunodeficiency virus (HIV) and AIDS was not collected in any year. To calculate death rates and the case-fatality rate, we included deaths that occurred during hospitalization or during the episode of illness if the patient was not hospitalized.

Streptococcus pneumoniae isolates were serotyped using type-specific antisera and observation of the Quellung reaction at the Centers for Disease Control and Prevention or the Minnesota Department of Health. For analysis, pneumococcal serotypes were grouped as follows: PCV-7 serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F), which are also in the polysaccharide vaccine; serotypes only in the polysaccharide vaccine (1, 2, 3, 5, 7F, 8, 9N, 10A, 11A, 12F, 15B, 17F, 19A, 20, 22F, and 33F); and all other serotypes and nontypeable pneumococci (not included in either vaccine). For rate calculations, case-patients missing serotype results were distributed according to those with known serotypes from the same year, age group, and surveillance area.

Crude and age-specific incidence rates were calculated using either Census data (2000) or postcensal population estimates as denominators (1998–1999, 2000–2002). Standardized rates were directly standardized to the 2000 US population. Race/ethnicity information was collected because of the documented differences in disease risk between whites and blacks. Race/ethnicity–specific, standardized, and estimated rates were calculated using single-race “bridged” postcensal population estimates for denominators; for 2002-2003, case-patients were grouped by single race/ethnicity categories using the same method.7 Case-patients missing information on race/ethnicity were distributed according to those with known race from the same age group, year, and surveillance area.

We used SAS version 9.1 (SAS Institute Inc, Cary, NC) for statistical analysis. Changes in incidence between periods were assessed by comparing rates from later periods with 1998-1999 rates as relative risks. These were reported as percentage changes (relative risk –1) × 100) in rates between the 2 periods, together with associated P values and 95% confidence intervals (CIs). P<.05 was considered statistically significant. Proportions were compared using the χ2 test and χ2 test for trend. Univariate and multivariable logistic re-
gression, including cases from 2000-2003 (when all surveillance areas collected comorbidity data), were used to assess the association of several patient and disease characteristics with the outcome of death.

**RESULTS**

**Overall Changes in Disease Burden**

Between 1998 and 2003, 9934 cases of invasive pneumococcal disease were reported among persons aged 50 years or older; 88.8% had an isolate available for serotyping, and 91.5% had race reported. Crude annual rates of invasive disease were 40.6, 41.0, 38.1, 33.0, 29.3, and 29.6 cases/100 000 adults aged 50 years or older in 1998 through 2003, respectively. Among 4 age groups (50-64, 65-74, 75-84, and ≥85 years), rates of invasive disease increased with older age (Figure). Within each of these age groups, incidence declined significantly between 1998-1999 and 2002-2003; declines ranged from −1% (95% CI, −24% to −11%) for those aged 50 through 64 years to −35% (95% CI, −41% to −28%) for those aged 75 through 84 years.

The incidence of invasive pneumococcal disease decreased equally between 1998-1999 and 2002-2003 among men and women aged 50 years or older (−28%). Although incidence was higher among blacks than whites in this age group, percentage declines were similar; among blacks, incidence decreased from 72.1 to 51.3 cases/100 000 (−29%) and among whites from 37.4 to 26.8 cases/100 000 (−28%). In 2002-2003, incidence among blacks aged 50 through 64 years (49.7 cases/100 000) was significantly higher than that among blacks aged 65 through 74 years (39.4 cases/100 000; relative risk, 1.26; 95% CI, 1.02 to 1.56).

In 2002-2003, standardized rates of invasive disease were significantly lower than those in 1998-1999 in each surveillance area except California (41.8 and 41.2 cases/100 000 in 1998-1999 and 2002-2003, respectively). Among the 7 other surveillance areas, changes in standardized rates ranged from 24% declines in Tennessee (95% CI, −33% to −12%; from 40.8 to 31.2 cases/100 000) and in Minnesota (95% CI, −33% to −13%; from 39.1 to 29.8 cases/100 000) to −37% in New York (95% CI, −48% to −22%; from 36.9 to 23.4 cases/100 000).

Rates in children younger than 5 years, the conjugate vaccine’s target age group, were examined for comparison. Rates in children in this age group were higher at baseline than rates in older adults and changed more dramatically. In 1998-1999, the mean annual incidence of invasive pneumococcal disease among children younger than 5 years was 95.3 cases/100 000. The rate for 2000-2001 was 61.4 cases/100 000 (−36%; 95% CI, −40% to −31%) and for 2002-2003 was 24.2 cases/100 000 (−75%; 95% CI, −77% to −72%).

### Changes in Invasive Disease by Pneumococcal Serotype

Among adults aged 50 years or older, the incidence of invasive pneumococcal disease caused by PCV-7 serotypes decreased from 22.4 to 10.2 cases/100 000 (−55%; 95% CI, −58% to −51%) and for serotype 14. There were significant changes in incidence of disease caused by 3 other commonly occurring serotypes, including increases in disease caused by serotypes 3 (21%; 95% CI, 2% to 44%) and 19A (38%; 95% CI, 10% to 73%) and a decrease in disease caused by serotype 12F (−53%; 95% CI, −64% to −38%).

### Disease Syndromes

Invasive pneumonia, bacteremia without a focus, and meningitis were the most common invasive pneumococcal disease syndromes in adults aged 50 years or older (Table 2). Invasive pneumonia alone accounted for 73.2% of all 9934 cases, invasive pneumonia plus meningitis for 1.3%, meningitis alone for 3.6%, bacteremia without a focus for 21.1%, and other invasive disease syndromes for 2.9%. The mean annual incidence of meningitis among those in this age group did not change significantly.
Between 1998-1999 and 2002-2003, changes in incidence of these common disease syndromes varied by the serotype causing the illness (Table 2). In 2002-2003, a 38% (95% CI, −57% to −11%) reduction in meningitis incidence caused by PCV-7 serotypes was offset by a 131% (95% CI, 50% to 255%) increase in disease caused by serotypes not in either vaccine, such that the overall incidence of meningitis was unchanged. Both in 2000-2001 and in
2002-2003 (vs 1998-1999), incidence of bacteremia without a focus declined significantly in each of the 3 serotype categories; this decline was greatest in 2002-2003 for bacteremia caused by PCV-7 serotypes (−77%; 95% CI, −81% to −72%). The rate of invasive pneumonia caused by PCV-7 serotypes declined significantly between 1998-1999 and 2002-2003 (−48%; 95% CI, −52% to −43%); disease caused by serotypes only in the polysaccharide vaccine increased (11%; 95% CI, 1% to 22%), as did invasive pneumonia caused by serotypes not in either vaccine (26%; 95% CI, 9% to 45%).

Comorbid Conditions Among Cases
Between 1998-1999 and 2002-2003, the proportion of case-patients with certain comorbid conditions increased (Table 3). Notably, the proportion of case-patients aged 50 years or older reported to have HIV infection increased from 1.7% (47/2737) in 1998-1999 to 5.6% (124/2231) in 2002-2003 (P<.001). Most case-patients with HIV infection were aged 50 through 64 years; 4.9% (43/878) of case-patients in this age group had HIV infection in 1998-1999 and 13.5% (119/881) in 2002-2003 (P<.001). In the California surveillance area (San Francisco County), the proportion of case-patients aged 50 years or older with reported HIV infection increased from 5.6% (11/198) to 15.8% (29/184) (P=.001). Proportionally more episodes of invasive pneumococcal disease were caused by non–PCV-7 serotypes among HIV-infected patients (60.6% [140/231]) compared with illnesses caused by the same serotypes among other case-patients (51.3% [3323/6474]) (P=.006). In 2002-2003 (vs 1998-1999), significantly higher proportions of case-patients aged 50 years or older were reported to have received recent immunosuppressive therapy or to have had diabetes or chronic obstructive pulmonary disease (Table 3). However, the proportion of case-patients with heart failure did not change and that of those with nephrotic syndrome decreased.

Over the study period, the proportion of case-patients with at least 1 chronic condition that is an indication for pneumococcal polysaccharide vaccine (including immunocompromising conditions and certain other comorbid conditions) (Table 3) increased from 62.3% (1842/2955) to 72.0% (1721/2390) (P<.001).

Mortality
Rates of death among adults aged 50 years or older following an episode of invasive pneumococcal disease decreased from 6.9 deaths/100 000 in 1998-1999 to 5.7 in 2002-2003 (−18%; 95% CI, −27% to −9%), a smaller decrease than the overall decline in disease incidence (−28%; 95% CI, −31% to −24%). According, the case-fatality rate increased.
from 15.7% in 1998 to 18.7%, 16.4%, 20.4%, 19.4%, and 19.5% in the 5 subsequent years, respectively ($\chi^2$ test for trend, $P$ = .001). Factors significantly associated with death in univariate analyses were age 75 years or older; disease syndromes of meningitis or bacteremia without focus; presence of 1 or more immunocompromising conditions or 2 or more other chronic conditions; surveillance area; and year (Table 4). In addition, case-fatality rates were significantly higher among individuals with disease caused by serotypes 19F, 23F, 3, or 11A, and lower for those with disease caused by serotype 12F, each in comparison with the case-fatality rate for disease caused by serotype 14. Multivariable analysis showed that each of these factors was independently correlated with the risk of death, as was disease caused by serotypes 19F, 23F, 3, or 11A (Table 4).

**US Disease Burden**
Among persons aged 65 years or older, the standardized rate of invasive pneumococcal disease was 41.7 cases/100 000 in 2002-2003. Among whites and blacks in this age group, age-standardized rates were 41.2 and 54.7 cases/100 000, respectively. Projecting standardized rates to the US population aged 50 years or older, we estimated that an annual average of 29 800 cases of invasive pneumococcal disease and 5100 deaths occurred in this age group in 1998-1999. For 2002-2003, we estimated 23 600 cases and 4500 deaths per year—6250 fewer cases and 550 fewer deaths per year among Americans aged 50 years or older, compared with the years prior to introduction of the conjugate vaccine.

**COMMENT**
Our findings indicate that the early decrease noted in invasive disease in older adults following conjugate vaccine licensure for children in 2000 has continued through 2003. During 2002 and 2003, the overall rate of invasive disease among persons aged 65 years or older (41.7 cases/100 000) surpassed the Healthy People 2010 goal of 42 cases/100 000. The rate among blacks (54.7 cases/100 000) was lower than in earlier years but did not reach this goal. In just 2 years, 2002 and 2003, we estimate that 12 500 fewer cases and 1100 fewer deaths occurred among older Americans, compared with the numbers of cases and deaths occurring before the vaccine was available.

Several factors support the hypothesis that the declines in invasive disease reported here likely occurred because of decreased community transmission of vaccine-type pneumococci from young children, many of whom have received PCV-7. Studies of pneumococcal carriage indicate that conjugate vaccines reduce carriage of vaccine-type pneumococci in vaccinated children. Likewise, unvaccinated children in close contact with vaccinated children or living in communities in which the vaccine is being used also have experienced reductions in pneumococcal carriage and disease caused by PCV-7 serotypes. In this analysis, the overall decline in invasive disease incidence was mainly due to a decrease in disease caused by PCV-7 serotypes, suggesting a specific conjugate vaccine
effect. In addition, the timing of the changes among older adults coincided with uptake of vaccine in children; incidence first declined in 2001, following initial use of PCV-7 among young children in the last half of 2000, and then dropped further in 2002-2003 as vaccine coverage in children increased. Our findings are unlikely to represent an isolated temporal downturn in incidence. Other reports of ABCs data from earlier years documented rates of invasive pneumococcal disease similar to those in our baseline years of 1998 and 1999: 55.9 cases/100,000 among adults aged 60 years or older in 1995 and 23.5 and 61.7 cases/100,000, respectively, among those aged 50 through 64 years and 65 years or older in 1997. Preliminary data suggest that the rate for adults aged 50 years or older was approximately 27.2 cases/100,000 in 2004 (CDC, unpublished data), similar to our reported rate for 2003.

The dramatic changes we report were seen during a period when vaccine coverage among young children was still incomplete. The primary series for PCV-7 calls for vaccination of infants at ages 2, 4, and 6 months, with a fourth dose between ages 12 and 18 months. However, vaccine was in short supply from August 2001 through May 2003, and many children received fewer doses than the full series. The National Immunization Survey first estimated PCV-7 coverage for children born in August 1998 through November 2000; most of these children were born before the vaccine was licensed, and only 11% (SD, 0.7%) had received 3 or more doses of PCV-7 by age 24 months. Coverage increased to 67.7% (SD, 1.2%) for those born in August 2000 through November 2002, a period after the vaccine was licensed. Vaccine coverage estimates varied considerably among the areas sampled, and we were unable to directly compare coverage in our ABCs areas with declines in disease rates because of limited overlap in the 2 systems. How much vaccine coverage is needed for indirect effects on disease to occur remains a key question. A model evaluating this question for *Haemophilus influenzae* type b conjugate vaccine showed that much of the decline in invasive disease could be attributed to indirect effects of the vaccine, even at relatively low levels of vaccine coverage.

Some may wonder whether some of the change in disease rates could be attributable to recent increases in use of polysaccharide vaccine in the United States. Among all states and several US territories, the Behavioral Risk Factor Surveillance System reported that the median proportion of persons aged 65 years or older who remembered ever having received polysaccharide vaccine increased from 45.8% in 1997 to 62.9% in 2002. However, increased polysaccharide vaccine coverage was not likely to have been a major cause of the disease declines reported here. First, rates stratified by serotype showed no decrease in invasive disease caused by serotypes included only in the polysaccharide vaccine. Second, polysaccharide vaccine is used primarily in adults aged 65 years or older, and immunity after vaccination is thought to wane over 5 to 10 years. We reported significant declines among those aged 50 through 64 years, an age group less likely to have been vaccinated, and among those aged 85 years or older, a group less likely to have retained full immunity if vaccinated before age 75 years. Third, one model estimated that among adults aged 65 years or older, a substantial increase in polysaccharide vaccine coverage (from 45% to 90%) would decrease incidence of invasive disease by 12%, at most, from 1998 rates. Here, rates in those aged 65 years or older decreased by 30% between 1998-1999 and 2002-2003, with polysaccharide vaccine coverage still below 90%.

Healthy adults may be benefiting more than chronically ill adults from the introduction of PCV-7 for children. The relative frequency of several comorbid conditions, including diabetes and immunocompromising conditions, increased among patients with invasive pneumococcal disease over the reporting period. Most notably, the proportion of those aged 50 through 64 years with HIV infection increased more than 2-fold, from 4.9% in 1998-1999 to 13.5% in 2002-2003. Several factors could be influencing the changing frequency of comorbid conditions among case-patients. First, an increasing prevalence of chronic illnesses in the general population could have influenced these results. Second, fewer PCV-7 serotypes and more non–PCV-7 serotypes were circulating as colonizing strains in 2002 compared with 2000. Persons with immunocompromising conditions or other comorbid conditions may be more susceptible to invasive disease caused by certain serotypes in comparison with healthier individuals. In the conjugate vaccine era, targeting persons with chronic conditions for receipt of polysaccharide vaccine remains a useful strategy for reaching those at highest risk for invasive disease. Although incidence of death following invasive pneumococcal disease declined, the case-fatality rate increased somewhat between 1998-1999 and 2002-2003. This finding likely reflects the higher proportion of case patients with comorbid conditions in the later time period. Multivariable analysis found that those with any immunocompromising conditions and with 2 or more other chronic conditions were more likely to die from their pneumococcal infections than were healthier persons; comorbid conditions have been shown to be associated with mortality from invasive pneumococcal disease in several other studies. Risk of death was also independently associated with age 75 years or older, disease syndromes of meningitis and bacteremia without focus, and invasive disease caused by certain serotypes (19A, 23F, 11A, and 3). Two other studies have shown serotype 3 to be associated with excess mortality, and in the polysaccharide vaccine, serotype 3 has been shown to have relatively poor immunogenicity for patients aged 65 years or older with chronic conditions. Therefore, an expanded valent conjugate vaccine would be expected to provide even more benefit to elderly persons.
gate vaccine that included serotype 3 may be of additional benefit to older adults if it could reduce transmission of this serotype.

When we examined changes in disease rates by syndrome, we found that incidence of bacteremia without a specific focus declined earlier and to a greater extent than that of pneumonia. For meningitis, an increase in disease caused by nonvaccine serotypes erased the benefit of a decrease in meningitis caused by PCV-7 serotypes. The reasons behind the different changes in rates for the 3 syndromes are not entirely clear. This differential effect by syndrome may in part be caused by differences in the propensity of various serotypes to cause one type of disease manifestation rather than another. Rates of bacteremia without a focus decreased the most for disease caused by PCV-7 vaccine serotypes, but changes were also seen for disease caused by serotypes only in the polysaccharide vaccine and for nonvaccine serotypes. This suggests that, at least for bacteremia, some other secular trend was playing a role.

We observed small but statistically significant increases in incidence of disease caused by nonvaccine serotypes, and that caused by non–PCV-7 serotypes, between 1998-1999 and 2002-2003. These increases included invasive disease caused by serotypes not in either vaccine among those aged 50 through 64 years (36%); invasive pneumonia caused by serotypes only in the polysaccharide vaccine (11%) and by other serotypes (26%); meningitis caused by serotypes not included in either vaccine (131%); and invasive disease caused by serotypes 3 (21%) and 19A (38%). Overall, decreases in invasive disease caused by PCV-7 serotypes far outweighed increases in disease caused by nonvaccine serotypes, and the degree of these increases was not as striking in this population of older adults as that shown among adults with HIV or AIDS in another ABCs study. Nonetheless, as the pneumococcus has repeatedly shown its ability to adapt, the amount of disease caused by non–PCV-7 serotypes bears watching.

A strength of this study was the reporting of changes in population-based rates, made possible because invasive disease was monitored using standardized methods in a large population base over several years. Serotyping of isolates enabled an exploration of possible causes for the observed changes. In addition, the large number of cases identified enabled us to evaluate trends in important subgroups.

Our study also has limitations. First, records of polysaccharide vaccination status of case patients were largely unavailable in hospital records, and therefore these data were too incomplete to include in this analysis. Second, reporting of comorbid conditions may have been somewhat inconsistent among cases because of differences in medical records among institutions and because multiple staff completed case reports. Nonetheless, the methods for evaluating underlying conditions remained constant over the study period, so any inconsistencies should not have affected the trend analysis. Another limitation of our data is that they are descriptive, so we cannot definitively link the use of PCV-7 to our observed findings. However, reductions in disease (1) were limited to the PCV-7 serotypes, (2) were temporally associated with initial and increasing PCV-7 uptake, and (3) have persisted over several years (through 2004), suggesting that use of the vaccine in children was the primary reason for these declines.

We have documented a consistent decrease in incidence of invasive pneumococcal disease in an age group at high risk for serious disease and death from these illnesses. Policy makers elsewhere who are considering whether to incorporate PCV-7 into their routine infant immunization programs and who are weighing its cost-effectiveness should consider the benefits seen in older adults. However, it is unknown whether this herd effect will be similar in all settings and population subgroups. The size of the effect may differ in populations with different serotype distributions or with a higher or lower prevalence of chronic conditions among older adults. We look forward to results from other populations to see if similar effects will occur. In the US population, use of PCV-7 for children has been an effective means of preventing disease in older adults.

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