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Decreases in Case-Fatality and Mortality Rates for Invasive Pneumococcal Disease in Olmsted County, Minnesota, during 1995–2007: A Population-Based Study

Constantine Tsigrelis[1], **Imad M. Tleyjeh**[1,4], **Brian D. Lahr**[2], **Lisa M. Nyre**[3], **Abinash Virk**[1], and **Larry M. Baddour**[1]

1*Department of Medicine, Division of Infectious Diseases, Mayo Clinic, Rochester, Minnesota*

2*Department of Health Sciences Research, Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota*

3*Department of Laboratory Medicine and Pathology, Division of Microbiology, Mayo Clinic, Rochester, Minnesota*

4*Department of Medicine, Division of Infectious Diseases, King Fahd Medical City, Riyadh, Saudi Arabia*

Abstract

Background—Following the introduction of a 7-valent pneumococcal conjugate vaccine for children in 2000, there has been a decrease in the incidence of invasive pneumococcal disease among both children and adults in the United States. We evaluated the hypothesis that the case-fatality and mortality rates for invasive pneumococcal disease have also decreased since 2000.

Methods—We conducted a population-based outcome study in Olmsted County, Minnesota, during the period 1995–2007 that involved patients of all ages.

Results—From 1 January 1995 through 31 December 2007, a total of 180 eligible cases of invasive pneumococcal disease were identified in Olmsted County. During the 13-year study period, the overall case-fatality rate for invasive pneumococcal disease decreased from 19% (14 of 74 cases) in 1995–1999 to 5% (5 of 91 cases) in 2001–2007, an 83% decrease, after adjustment for age, sex, and Charlson comorbidity index score (P = .003). The largest decreases in case-fatality rate were seen among adults aged ≥65 years (an 86% decrease, from 31% [9 of 29 cases] to 8% [3 of 40 cases]; P =. 02) and patients with invasive pneumonia (a 78% decrease, from 22% [12 of 55 cases] to 7% [5 of 72 cases]; P = .01). The overall mortality rate for invasive pneumococcal disease decreased from 2.9 deaths per 100,000 person-years in 1995–1999 to 0.7 deaths per 100,000 person-years in 2001–2007, a 78% decrease, after adjustment for age and sex in a Poisson regression model (P = .002).

Conclusions—Significant decreases in the case-fatality and mortality rates for invasive pneumococcal disease were demonstrated in the population of Olmsted County. Additional studies are needed to confirm our findings in other populations.

After the introduction of a 7-valent pneumococcal conjugate vaccine (PCV-7) for children in early 2000 in the United States, an impressive decrease in the incidence of invasive pneumococcal disease (IPD) occurred [1-7]. The decrease in incidence of IPD occurred not only among children who had been vaccinated with PCV-7 [1-5], but also among infants [6],

Reprints or correspondence: Dr. Constantine Tsigrelis, Div. of Infectious Diseases, Mayo Clinic, 200 First St. SW, Rochester, MN 55905 (tsigrelis.constantine@yahoo.com).

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older children [2], and adults [7] who had not been vaccinated with PCV-7, possibly as a result of an indirect or "herd" effect of PCV-7 vaccination [8].

Outcomes of IPD have also changed since the introduction of PCV-7. The Active Bacterial Core (ABC) surveillance team from the Centers for Disease Control and Prevention reported an 18% decrease in the mortality rate for IPD among adults aged ≥50 years from 1998–1999 to 2002–2003 [7]. The case-fatality rate for IPD, however, increased from 15.7% in 1998 to 19.5% in 2003; this increase was possibly associated with an increased proportion of patients with comorbidities over time. Recent assessments of outcome of IPD in adults are lacking. In addition, to our knowledge, outcome studies of IPD in adults have not been performed in defined populations in the United States, other than the ABC population. Therefore, we conducted a population-based outcome study of IPD in Olmsted County, Minnesota, during the period 1995–2007 to further study mortality and case-fatality rates for IPD among adults.

METHODS

Population

Olmsted County (2000 census population, 124,277 persons) is located in southeastern Minnesota and includes the central city of Rochester (population, 85,806 persons) and the surrounding area [9]. Most of the population is white (90.3% white, according to the 2000 census) and of northern European ancestry. The demographic characteristics of Olmsted County residents resemble those of the white population of the United States, with the exception of a higher proportion of the working population employed in professional services, such as the health care industry (37.1% of Olmsted County residents, compared with 26.9% of the US white population in 2000) and correspondingly higher educational levels (91.1% of Olmsted County residents completed at least high school, compared with 83.2% of the US white population in 2000) [9].

One unique feature of Olmsted County is that medical care is mainly self-contained in the community [9-12]. This is because of the relative geographic isolation of Olmsted County from other urban centers and because local residents have access to every medical and surgical specialty at the Mayo Clinic. The closest competing medical centers are located in Minneapolis, Minnesota (139 km to the north); LaCrosse, Wisconsin (114 km to the east); Iowa City and Des Moines, Iowa (317 and 333 km to the south, respectively); and Sioux Falls, South Dakota (376 km to the west). Furthermore, the population is relatively stable, particularly for older age groups [12]; for example, the median length of follow-up available for residents aged 50–59 years is 29 years [12].

Another unique feature of Olmsted County is that nearly all medical care is delivered to local residents by only a few providers, including the Mayo Clinic and Olmsted Medical Center. This allows for review of the original medical records from all health care providers in the community [9]. This unique setting allows for essentially complete ascertainment of all cases of a specific disease among residents of Olmsted County and thus constitutes an ideal environment for population-based incidence and outcome studies [9].

Population-based studies are conducted in Olmsted County using the Rochester Epidemiology Project, which is a medical records–linkage system that has received federal funding since 1966 [9]. The Rochester Epidemiology Project links virtually all sources of medical care available to the local population of Olmsted County. For each resident of Olmsted County, researchers are able to learn which local health care providers the patient visited and then to review the original inpatient and outpatient medical records.

Case definition

IPD was defined as the isolation of *Streptococcus pneumoniae* from a culture of a specimen from a normally sterile site (including cultures of blood, CSF, pleural fluid, peritoneal fluid, bone or joint fluid, and other normally sterile site specimens) [1]. Olmsted County residents of all ages were included as subjects.

Case ascertainment

Cases of IPD were identified via computerized databases from the only 2 microbiology laboratories in Olmsted County: the Mayo Clinic and Olmsted Medical Center microbiology laboratories. All cultures (from all sources) that were positive for *S. pneumoniae* for patients of all ages were identified for the period 1 January 1995 through 31 December 2007, and the residency of each patient at the time of diagnosis of IPD was determined by a residency specialist from the Rochester Epidemiology Project. The medical record of each Olmsted County resident with a positive culture from a sterile source was reviewed by the primary investigator (C.T.) to confirm the IPD diagnosis and the residency status of the patient at the time of diagnosis.

We excluded patients who did not provide permission for use of their medical records for research. We also excluded patients whose *S. pneumoniae*–positive cultures involved specimens obtained during autopsy; however, there were only 5 autopsy cases reviewed in our study, and none of the patients were found to have *S. pneumoniae* in specimens isolated from a normally sterile site. Polymicrobial blood cultures that yielded *S. pneumoniae* were excluded, except in cases in which the patient had a syndrome consistent with IPD and in which the other organism(s) growing in the blood cultures were considered to be contaminants (including *Propionibacterium*, *Micrococcus*, *Rothia*, and *Corynebacterium* species and coagulase-negative staphylococci). The institutional review boards at Mayo Clinic and Olmsted Medical Center approved the study and waived the requirement for informed consent.

Data collection and definitions

The Mayo Clinic microbiology department used the Bactec 9240 automated blood culture system (Becton Dickinson Diagnostic Instrument Systems) during 1995–2007. The Olmsted Medical Center microbiology department used Septi-Chek manual bottles (PML Microbiologics) during 1995–2000 and the Bactec 9050 automated blood culture system (Becton Dickinson Diagnostic Instrument Systems) during 2001–2007.

For the calculations of the mortality and case-fatality rates, deaths were considered to have occurred if the patient died during hospitalization or, if the patient was not hospitalized, during the episode of illness [7]. The case-fatality rate was defined as the number of deaths due to IPD divided by the total number of cases of IPD. To quantify a score of one's lifetime acquisition of comorbidities up to the time of IPD diagnosis, the Charlson comorbidity index score was calculated using diagnosis code databases established by the Rochester Epidemiology Project [13].

Statistical analysis

For calculating mortality rates for IPD, the entire population of Olmsted County was considered to be at risk of infection. The denominators of age- and sex-specific person-years were derived from decennial census figures. For years after the most recent decennial census in 2000, a population growth rate of 1.9% was used to project these numbers. Rates were adjusted by age and sex to the population of white persons in the United States in 2000.

Poisson regression was used to determine the temporal, age-associated, and sex-associated effects on the mortality rate for IPD. Each of these prognostic factors was treated as categorical

and was included in a multivariate model. The time covariate was categorized into pre-PCV-7 and PCV-7 periods so that the mortality rates of IPD before and after introduction of PCV-7 could be compared. The pre-PCV-7 period was defined as 1 January 1995 through 31 December 1999, whereas the PCV-7 period was defined as 1 January 2001 through 31 December 2007. A 1-year transition period was defined as 1 January 2000 through 31 December 2000 to allow for PCV-7 uptake; data from this period were excluded from the analysis [6]. The case-fatality rate was compared between the pre-PCV-7 and PCV-7 periods by a logistic regression model that adjusted for age, sex, and Charlson comorbidity index score. The level of significance for statistical testing was $P<.05$ (2-sided). All analyses were performed using SAS software, version 8 (SAS Institute).

RESULTS

During the period 1 January 1995 through 31 December 2007, a total of 191 cases of IPD were identified among Olmsted County residents. Eleven patients with IPD (9 with blood culture isolates and 1 each with CSF and ankle joint culture isolates) who refused authorization to use their medical records for research were excluded. Therefore, 180 (94%) of the 191 IPD cases were available for review.

The outcome data are summarized in table 1. During the 13-year study period, the overall case-fatality rate for IPD was 12%, with the highest case-fatality rates observed among adults aged ≥65 years (19%) and among patients with invasive pneumonia (14%). The temporal trends in outcome of IPD are summarized in table 2. The overall case-fatality rate for IPD decreased from 19% during 1995–1999 to 5% during 2001–2007, an 83% decrease, after adjustment for age, sex, and Charlson comorbidity index score in a logistic regression model (OR, 0.17; 95% CI, 0.05–0.55; $P = .003$). The greatest decreases in the case-fatality rate were noted for adults aged ≥65 years and for patients with invasive pneumonia; the case-fatality rate decreased from 31% during 1995–1999 to 8% during 2001–2007 among adults aged ≥65 years, an 86% decrease, after adjustment for age, sex, and Charlson comorbidity index score (OR, 0.14; 95% CI, 0.03–0.68; $P = .02$), and from 22% during 1995–1999 to 7% during 2001–2007 among patients with invasive pneumonia, a 78% decrease, after adjustment for age, sex, and Charlson comorbidity index score (OR, 0.22; 95% CI, 0.07–0.72; $P = .01$).

There was no significant difference in the Charlson comorbidity index scores for IPD cases from 1995–1999 (median score, 2) and from 2001–2007 (median score, 3; $P = .22$, by Wilcoxon rank-sum test). There was no significant difference in the number of patients who died of IPD who were up to date with a 23-valent pneumococcal polysaccharide vaccination (PPV-23) in 1995–1999 (4 [36%] of 11 patients), compared with 2001–2007 (3 [75%] of 4 patients; $P = .28$, by Fisher's exact test. Three deaths that occurred during 1995–1999 and 1 death that occurred during 2001–2007 were excluded from the analysis because the patients had unknown PPV-23 status; up-to-date PPV-23 status was based on the recommended adult immunization schedule of the Advisory Committee on Immunization Practices [14].

DISCUSSION

In this geographically defined population, dramatic changes in the outcome of invasive pneumococcal disease occurred during the past 13 years. We observed a significant decrease in the overall case-fatality rate for IPD, and this was primarily explained by a decrease in the case-fatality rate among adults aged ≥65 years and among patients with invasive pneumonia. In addition, we observed a significant decrease in the mortality rate for IPD over time.

Multiple factors may explain the decreases in the case-fatality and mortality rates for IPD in Olmsted County. Age, sex, and Charlson comorbidity index score were included in our logistic

regression model and did not affect the significant association between time and case-fatality rate. Increasing PPV-23 coverage over time and/or PCV-7 coverage (via a herd effect of PCV-7 in adults) may have led to less-severe disease among patients and could have affected the case-fatality rate for IPD. Although we did not know PPV-23 vaccination rates for Olmsted County, estimated PPV-23 coverage among adults aged ≥65 years in Minnesota (based on the Behavioral Risk Factor Surveillance Survey data) increased significantly over time, from 40% in 1995, to 52% in 1999, and to 71% in 2006 [15]. Among the patients who died of IPD in our study, we did not observe a significant difference in the number of patients who were up to date with PPV-23 vaccination for 1995–1999 versus 2001–2007; however, the absolute numbers were low. Estimated PCV-7 coverage (i.e., receipt of ≥3 doses) in Minnesota (based on National Immunization Survey data) also increased significantly over time, from 48% in 2002, to 77% in 2004, and to 93% in 2006 [16]. Other factors that may have affected the case-fatality rate for IPD over time include improved hospital care, more rapid antibiotic administration in patients with suspected pneumonia, changes in severity of illness, and/or changes in pneumococcal serotype, although these variables were not measured in our study.

The ABC surveillance team previously published data on the outcome of IPD in adults. They reported a decrease in the mortality rate for IPD (from 6.9 deaths per 100,000 persons in 1998–1999 to 5.7 deaths per 100,000 persons in 2002–2003) in the United States among adults aged ≥50 years; however, the case-fatality rate increased from 15.7% in 1998 to 19.5% in 2003 [7]. The increase in the case-fatality rate was thought to be related to a higher proportion of patients with comorbidities over time. A recent update using the ABC surveillance database reported an overall IPD case-fatality rate of 10.3% (6500 estimated deaths among 63,067 estimated cases) in 1997–1999, which increased to an overall IPD case-fatality rate of 11.7% (4850 estimated deaths among 41,550 estimated cases) in 2005 ($P<.001$, by χ^2 test) [17]. The reason for the significant difference between the changing case-fatality rate over time in the Olmsted County population (i.e., a decreased IPD case-fatality rate) versus the ABC surveillance population (i.e., an increased IPD case-fatality rate) is not clear; however, many variables probably contribute, including increasing comorbidities in the ABC surveillance population, the different populations studied, and different methods of both case and death ascertainment.

Our study has several important strengths. First, we report IPD outcome data in a different population than the ABC surveillance group; thus, our data may be compared with data for other populations in the United States that are similar to the Olmsted County population. Second, our study was performed in a geographically isolated population in a region where medical care is mainly self-contained in the community, thus allowing essentially complete ascertainment of all IPD cases and accurate outcome data. Incomplete case ascertainment is a potential problem in studies that rely on disease reporting. Third, all original inpatient and outpatient medical records were available for review, allowing us to abstract accurate outcome data. Finally, our study was performed during a 13-year period in a stable population using consistent data abstraction methods.

Our study also has several potential limitations. First, the Olmsted County population is similar to the US white population, and our findings should only be generalized to similar populations in the United States. Second, given the low number of deaths in our study ($n = 19$), we could not analyze other variables in the logistic regression model that may have been associated with case fatality (such as pneumococcal vaccination and individual comorbidities). Third, although we demonstrated significant decreases in the case-fatality and mortality rates for IPD in Olmsted County, we were unable to study all potential variables that could account for these changes. Additional prospective observational studies are necessary for additional study of these variables. Fourth, although data for 180 (94%) of 191 patients with IPD were available for review, the remaining 11 patients (6%) with IPD did not authorize use of their records for

research. This is an unavoidable source of potential bias in all studies, and it could have affected our results if a disproportionate number of patients with IPD who had not authorized the use of their records died in the later time period, although this would be unlikely. Finally, although the culture methods at Mayo Clinic microbiology laboratory remained the same during the 13-year period, the Olmsted Medical Center microbiology laboratory changed from a manual blood culture system to an automated system in 2001; however, this did not likely have a major effect on the number of IPD cases detected.

In conclusion, we observed a significant decrease in the overall case-fatality rate for IPD from 1995–1999 to 2001–2007 in Olmsted County, with the greatest decreases noted among adults aged ≥65 years and among those with invasive pneumonia. In addition, the mortality rate for IPD decreased during these intervals. These findings are novel and deserve additional investigation.

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Table 1

Outcomes of cases of invasive pneumococcal disease, 1995–2007.

Outcome variable	Value
Overall case-fatality rate	21/180 (12)
Case-fatality rate, by age group	
≥65 years	14/75 (19)
40–64 years	4/45 (9)
20–39 years	2/24 (8)
5–19 years	1/9 (11)
<5 years	0/27 (0)
Case-fatality rate, by clinical syndrome	
Invasive pneumonia	19/136 (14)
Meningitis	1/13 (8)
Bacteremia without a focus	1/24 (4)
Other syndromes[a]	0/7 (0)
Overall crude mortality rate[b]	1.3
Adjusted overall mortality rate[b,c]	1.6

NOTE. Data are proportion of cases (%), unless otherwise indicated.

[a] Other syndromes included otitis media ($n = 3$), prosthetic joint septic arthritis ($n = 2$), native joint septic arthritis ($n = 1$), and primary peritonitis ($n = 1$).

[b] Rate is expressed as no. of deaths per 100,000 person-years.

[c] Adjusted overall mortality rate is age- and sex-adjusted to the 2000 US white population.

Table 2

Temporal trends in the outcome of invasive pneumococcal disease.

Outcome variable	Period	
	1995–1999 (*n* = 74)	2001–2007 (*n* = 91)
No. of deaths	14	5
Overall case-fatality rate, %[a]	19	5
Case-fatality rate by age group		
≥65 years[a]	9/29 (31)	3/40 (8)
40–64 years	2/11 (18)	2/30 (7)
20–39 years	2/14 (14)	0/9 (0)
5–19 years	1/5 (20)	0/3 (0)
<5 years	0/15 (0)	0/9 (0)
Case-fatality rate, by clinical syndrome		
Invasive pneumonia[a]	12/55 (22)	5/72 (7)
Meningitis	1/5 (20)	0/6 (0)
Bacteremia without a focus	1/12 (8)	0/8 (0)
Other syndromes	0/2 (0)	0/5 (0)
Adjusted overall mortality rate[b,c]	2.9	0.7

NOTE. Data are proportion of cases (%), unless otherwise indicated.

[a] A significant difference was detected by a logistic regression model after adjustment for age, sex, and Charlson comorbidity index score.

[b] The adjusted overall mortality rate has been age- and sex-adjusted to the 2000 US white population and is expressed as no. of deaths per 100,000 person-years.

[c] $P = .002$ for the decrease in mortality rate from 1995–1999 to 2001–2007, after adjustment for age and sex in a Poisson regression model.