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TRENDS IN INVASIVE PNEUMOCOCCAL DISEASE AMONG OLDER ADULTS IN OLMSTED COUNTY, MINNESOTA

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Abstract

OBJECTIVE—Following the introduction of a 7-valent pneumococcal conjugate vaccine (PCV-7) for children in early 2000 in the United States, a decrease in the incidence of invasive pneumococcal disease (IPD) was seen in adults, likely due to a herd effect. However, there have been recent increases in IPD in adults caused by *Streptococcus pneumoniae* serotypes not included in PCV-7, so called "replacement disease". We performed a population-based study to further investigate this emerging concern.

METHODS—Population-based incidence study in Olmsted County, Minnesota, United States, in adults aged ≥ 50 years.

RESULTS—From 1/1/1995 to 12/31/2007, 104 cases of IPD were identified in Olmsted County in adults aged ≥ 50 years. We found a 45% increase in the incidence rate of IPD from 2001–2003 (17.7 cases per 100,000 person-years) to 2004–2007 (32.1 cases per 100,000 person-years) (p = 0.029). From 2002–2004 to 2005–2007, the incidence rate of IPD caused by *S. pneumoniae* serotypes not included in PCV-7 increased from 9.2 to 32.8 cases per 100,000 person-years (p<0.001).

CONCLUSION—A recent increase in the incidence of IPD in adults aged ≥ 50 years was demonstrated in Olmsted County, Minnesota due to serotypes not found in PCV-7. These findings are unique and merit further investigation.

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Keywords

Streptococcus pneumoniae; pneumococcal infections; incidence; aged; cohort studies

INTRODUCTION

Following the introduction of a 7-valent pneumococcal conjugate vaccine (PCV-7) for children in the United States in early 2000, a striking decrease in the incidence of invasive pneumococcal disease (IPD) occurred in vaccinated children.[1] Moreover, the incidence of IPD in adults also decreased, which was not a fully anticipated effect of PCV-7.[1–5] The decrease in IPD incidence in adults was thought to be due to an indirect or "herd" effect of PCV-7, caused by decreased transmission of pneumococci from young children to adults.[6]

Despite this, there has been a recent increase in the IPD incidence in adults caused by *S. pneumoniae* serotypes not included in PCV-7, so called "non PCV-7 serotypes" or "non-vaccine serotypes".[2–5] This phenomenon has been termed "replacement disease", and is postulated to be due to a reduction in nasopharyngeal colonization with PCV-7 type pneumococci leading to "replacement" and subsequent disease due to non PCV-7 type pneumococci.[2,6,7]

Although IPD caused by non PCV-7 serotypes has increased in adults, the magnitude of this increase has been low and only one study to date has demonstrated an increase in the overall incidence of IPD in adults from the pre PCV-7 period (before 2000) to the post PCV-7 period (after 2000). In that study performed in Alaskan Native adults aged ≥ 45 years, overall IPD incidence rates (expressed as cases per 100,000) increased from 56.6 in 1995–2000, to 74.2 in 2001–2003, to 80.9 in 2004–2006, while the IPD rate due to PCV-7 serotypes decreased from 14.5 to 13.4 to 4.3, and the IPD rate due to non PCV-7 serotypes increased from 32.3 to 53.5 to 71.2.[2]

The finding of an overall increase in incidence of IPD in adults due to non PCV-7 serotypes has only been described in one isolated population;[2] thus, additional investigation in other populations is warranted. Moreover, the epidemiology of IPD varies based on population. We therefore conducted a population-based incidence study of IPD in Olmsted County, Minnesota from 1995–2007 to assess for recent changes in the incidence of IPD in adults aged ≥ 50 years.

METHODS

Population

Olmsted County (population 124,277 according to 2000 census) is located in southeastern Minnesota and includes the central city of Rochester (population 85,806) and the surrounding area.[8] The demographic characteristics of Olmsted County residents (90.3% white according to 2000 census) resemble those of the US white population, with the exception of a higher proportion of the working population employed in professional services such as the health-care industry and correspondingly higher educational levels.[8]

There are several unique features of the Olmsted County population which allow for population-based studies to be performed. First, medical care is mainly self-contained within the community.[8–11] One reason for this is that Olmsted County is geographically isolated from other urban centers, the closest competing medical centers being in Minneapolis, Minnesota (87 miles to the north), LaCrosse, Wisconsin (71 miles to the east), Iowa City, Iowa (198 miles to the south), and Sioux Falls, South Dakota (235 miles to the west). An additional reason is that since the Mayo Clinic offers care in almost every medical and surgical specialty, local

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residents are not obliged to seek providers throughout a large region but are able to obtain their health care within the community.

A second unique feature of the Olmsted County population is that the majority of medical care is delivered to local residents by only a few providers, mainly the Mayo Clinic and Olmsted Medical Center. This allows for review of the medical records from all health care providers in the community. Review of medical records is accomplished by using the Rochester Epidemiology Project, a medical records-linkage system that has received federal funding since 1966.[8]

A final unique feature of the Olmsted County population is that it is relatively stable, particularly among older age groups.[9] For example, the median length of follow up available for residents aged 50 to 59 years is 29 years.[9] These unique features of the population allow for essentially complete ascertainment of all cases of a specific disease in residents of Olmsted County, and thus comprises an ideal environment for population-based incidence studies leading to accurate incidence data.[8]

Case and Serotype Definitions and Case Ascertainment

IPD was defined as the isolation of *S. pneumoniae* from a normally sterile site.[1] Cases of IPD were identified from computerized databases from the only 2 microbiology laboratories in Olmsted County: Mayo Clinic and Olmsted Medical Center microbiology laboratories. Olmsted County residents aged ≥ 50 years who developed IPD from 1/1/1995 through 12/31/2007 were included as cases. We excluded patients who did not give permission for use of their medical records. The institutional review boards at Mayo Clinic and Olmsted Medical Center approved the study and waived the requirement for informed consent.

Pneumococcal serotypes were defined as follows: 1) PCV-7 serotype (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F); 2) PCV-7 related serotype (serotypes 6A, 9A, 9L, 9N, 18A, 18B, 18F, 19A, 19B, 19C, 23A, and 23B); 3) 23-valent pneumococcal polysaccharide vaccine (PPV-23) serotype (serotypes 1, 2, 3, 5, 7F, 8, 10A, 11A, 12F, 15B, 20, 22F, and 33F); and 4) non-vaccine serotype (all other serotypes).[1]

Data Collection

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

Vaccination with PCV-7 began in Olmsted County in July 2000. Because PCV-7 and PPV-23 vaccination rates were not available for Olmsted County, survey data were used to estimate vaccination rates. For PPV-23 vaccination coverage among adults aged ≥ 65 years in Minnesota, Behavioral Risk Factor Surveillance Survey data of the Minnesota Department of Health were used.[12] For PCV-7 vaccination coverage among children 19–35 months of age in Minnesota, the National Immunization Survey data of the Centers for Disease Control and Prevention were used.[13] Clinical syndromes including meningitis, invasive pneumonia, and bacteremia without a focus have been previously defined.[4]

Statistical Analysis

For calculating incidence rates of IPD, the entire Olmsted County population aged ≥ 50 years was considered to be at risk for infection. The denominator age- and sex-specific person-years

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were derived from decennial census figures. For years after the last decennial census in 2000, a population growth rate of 1.9% was used to project these numbers. Rates were sex-adjusted to the population of whites in the United States in 2000. Only initial episodes of IPD were included as incident cases.

Poisson regression was used to examine the temporal and gender effects on the incidence rate of IPD for the overall group and for sub-groups defined by clinical characteristics. The time covariate was categorized into pre PCV-7 (1/1/1995 to 12/31/1999), immediate post PCV-7 (1/1/2001 to 12/31/2003), and distant post PCV-7 (1/1/2004 to 12/31/2007) periods so that the incidence rates of IPD before and after introduction of PCV-7 could be compared. A one year transition period was defined as 1/1/2000 to 12/31/2000 to allow for PCV-7 uptake, from which data were excluded in the analysis. If within a sub-group there were no incident IPD cases in males or females in at least one of the three time periods, a correction factor of 0.5 was applied to each stratum count so that regression estimates could be calculated.[14] The level of significance for statistical testing was defined as $p<0.05$ (2-sided). All analyses were performed using SAS version 8 software (SAS Institute Inc, Cary, NC).

RESULTS

From 1/1/1995 to 12/31/2007, 110 cases of IPD were identified in patients aged ≥ 50 years. For 6 of the IPD cases, authorization to use their medical records for research was refused by the patients or their authorized representatives. Therefore, 104 (95%) of the 110 IPD cases were available for review.

Demographic Characteristics

Of the 104 IPD cases, 53 (51%) were females and 51 (49%) were males. The median age was 74 years (range 50 years to 100 years). Of the 104 patients, 95 (91%) were Caucasian, 1 was Asian (1%), and 8 (8%) were of unknown race.

Incidence Rates

The incidence rate of IPD in patients aged ≥ 50 years (expressed as cases per 100,000 person-years) for the period 1995–2007 (including the transition period in 2000) was 25.6 overall, 23.7 in females, and 27.9 in males.

From 1995–1999 (pre PCV-7 period) to 2001–2003 (immediate post PCV-7 period), there was a non-significant decrease in the incidence rate of IPD from 24.5 to 17.7 cases per 100,000 person-years ($p = 0.260$) (Table 1). However, from 2001–2003 to 2004–2007 (distant post PCV-7 period), there was a 45% increase in the incidence rate of IPD from 17.7 to 32.1 cases per 100,000 person-years ($p = 0.029$) (Table 1).

Pneumococcal Serotypes

Pneumococcal serotype data were available for 50 (91%) of 55 IPD cases from 2002–2007. Serotype data prior to 2002 were not available. Of the 55 IPD cases from 2002–2007, 43 (78%) were due to non PCV-7 serotypes, 7 (13%) due to PCV-7 serotypes, and 5 (9%) due to unknown serotypes. The serotype distribution was as follows (serotypes listed in parentheses): PCV-7 serotype, 7 cases (4: n=4, 19F: n=1, 6B: n=1, 9V: n=1); PCV-7 related serotype, 17 cases (19A: n=6, 6A: n=6, 9N: n=3, 23A: n=2); PPV-23 serotype, 17 cases (3: n=6, 33F: n=3, 8: n=3, 22F: n=2, 20: n=1, 1: n=1, 11A: n=1); non-vaccine serotype, 9 cases (35F: n=3, 7C: n=2, 15A: n=2, 35B: n=1, 31: n=1); and unknown serotype, 5 cases.

From 2002–2004 to 2005–2007, there was a 72% increase in the incidence rate of IPD due to non PCV-7 serotypes ($p<0.001$) (Table 2). There were non-significant increases in incidence

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rates of IPD due to serotypes 19A and 3, both of which increased from 1 case per 100,000 person-years (19A: n=1, 3: n=1) in 2002–2004 to 4.8 cases per 100,000 person-years (19A: n=5, 3: n=5) in 2005–2007 (p = 0.10 for each serotype comparison between 2002–2004 and 2005–2007). For all other individual serotypes, absolute numbers were small and no significant changes were noted (Table 3).

Pneumococcal Vaccination

Of 97 patients eligible for PPV-23 vaccination who developed IPD from 1995–2007, 50 (52%) were up to date with PPV-23 vaccination at the time of IPD diagnosis (PPV-23 eligibility and up to date status based on Advisory Committee on Immunization Practices recommendations).[15]

Of 34 patients eligible for PPV-23 vaccination who developed IPD from 1995–1999, 15 (44%) were up to date with PPV-23 vaccination at the time of IPD diagnosis. Of 15 patients eligible for PPV-23 vaccination who developed IPD from 2001–2003, 8 (53%) were up to date with PPV-23 vaccination. Of 41 patients eligible for PPV-23 vaccination who developed IPD from 2004–2007, 25 (61%) were up to date with PPV-23 vaccination.

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, to 71% in 2006.[12] Based on the National Immunization Survey of the Centers for Disease Control and Prevention,[13] the estimated coverage with 3 or more doses of PCV-7 among children 19–35 months of age in the state of Minnesota was (yearly point estimate [%] +/− 95% confidence interval): 48.2 +/− 6.8 (2002), 72.9 +/− 6.7 (2003), 77.3 +/− 6.5 (2004), 86.6 +/− 5.3 (2005), 92.5 +/− 3.6 (2006), and 95.7 +/− 2.8 (2007).

Clinical Syndromes and Penicillin Susceptibility

Of 104 IPD cases from 1995–2007, 92 (88%) presented as invasive pneumonia, 5 (5%) bacteremia without a focus, 3 (3%) meningitis, 2 (2%) prosthetic joint septic arthritis, 1 (1%) native joint septic arthritis, and 1 (1%) purulent otitis media. Temporal trends in incidence rates of IPD by clinical syndrome are listed in Table 1.

Of 104 IPD isolates from 1995–2007, 81 (78%) were penicillin susceptible, 18 (17%) were penicillin non-susceptible, and 5 (5%) were of unknown penicillin susceptibility. There were no significant trends over time in penicillin susceptibility (Table 1).

Of the 6 IPD isolates from 2002–2007 that were of serotype 19A, 3 were penicillin susceptible and 3 were penicillin non-susceptible. Of the remaining isolates with available serotype data from 2002–2007, there were 7 isolates that were penicillin non-susceptible (serotypes 15A, 35B, 3, 8, 23A, 9V, and unknown serotype).

DISCUSSION

In this geographically defined population, we did not demonstrate a significant decrease in the incidence of IPD in adults aged ≥ 50 years following the introduction of PCV-7 in 2000. We did observe, however, a significant increase in the incidence of IPD in adults aged ≥ 50 years from 2001–2003 to 2004–2007, and this increase was due to *S. pneumoniae* serotypes not covered by PCV-7.

Although we observed a 28% decrease in the IPD incidence in adults aged ≥ 50 years from 1995–1999 to 2001–2003, this decrease was not statistically significant which could have been due, in part, to our sample size. The same reduction in IPD incidence was reported in adults aged ≥ 50 years from 1998–1999 to 2002–2003 in 8 metropolitan areas in the United States.

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[4] Other studies have shown similar decreases in IPD incidence: adults aged 40–64 years and ≥ 65 years from 1997–2000 to 2000–2004 in metropolitan Atlanta (25% and 26% decrease respectively),[3] Non-Native Alaskans aged ≥ 45 years from 1995–2000 to 2001–2003 (33% decrease),[2] and adults aged ≥ 65 years from 1998–1999 to 2004 in the United States (38% decrease).[5] In contrast, studies performed in Native American populations, specifically Alaskan Natives and White Mountain Apache persons in northern Arizona, did not show a decrease in the IPD incidence in adults after the introduction of PCV-7.[2,16]

Despite the decrease in incidence of IPD in adults after introduction of PCV-7, increasing incidence rates of IPD in adults due to non PCV-7 serotypes has been a concern.[2–5] We observed a 45% increase in the overall incidence rate of IPD in adults aged ≥ 50 years from 2001–2003 to 2004–2007, and this was driven by a 72% increase in the incidence of IPD due to non PCV-7 serotypes. Our finding is consistent with a study in Alaskan Natives which showed a 43% increase in the overall incidence rate of IPD in adults ≥ 45 years from 1995–2000 to 2004–2006, which was explained by a 121% increase in the incidence of IPD due to non PCV-7 serotypes.[2] Our findings are in contrast to Active Bacterial Core surveillance data which showed increases in the incidence of IPD due to non PCV-7 serotypes, but no overall increase in the incidence rate of IPD in adults from the pre PCV-7 period (before 2000) to the post PCV-7 period (after 2000).[3–5]

The reason for the recent increase in IPD incidence in adults in Olmsted County is unclear; however, there are a few potential explanations. It could be due to “replacement disease” caused by a reduction in nasopharyngeal colonization with PCV-7 type pneumococci from a herd effect of PCV-7 which led to “replacement” and subsequent disease due to non PCV-7 type pneumococci.[2,6] We cannot definitively make this conclusion because this is an ecologic study and we cannot link the introduction of PCV-7 with changes in IPD incidence. Furthermore, we do not have nasopharyngeal colonization data which could potentially support our findings. An alternate explanation of our findings is that the increase in IPD incidence in adults was not associated with the introduction of PCV-7, but was due to natural shifts in the incidence of IPD in the population.[17] While data regarding PPV-23 coverage among adults aged ≥ 50 years in Olmsted County were not available, statewide data indicate the vaccine coverage of PPV-23 among adults aged ≥ 65 years has increased over time. Therefore, a decrease in PPV-23 coverage is an unlikely explanation for this observation.

We also observed an increase in the incidence of IPD due to serotype 19A. This increase was not statistically significant however, likely due to the small sample size. This finding is consistent with prior studies that showed increasing incidence rates of IPD due to serotype 19A in adults over time.[3,5] This is troubling because serotype 19A has been characterized by antimicrobial resistance to multiple agents. Fifty-eight percent of IPD isolates were not susceptible to penicillin in one previous investigation among adults aged ≥ 65 years;[5] 50% (3/6) of the 19A isolates in our study were not susceptible to penicillin.

Our study has several important strengths. First, we describe IPD data in a population that is different from previously studied populations. Second, our study was performed in a geographically isolated population where medical care is mainly self-contained within the community, thus allowing for essentially complete case ascertainment and accurate incidence data. Third, all original inpatient and outpatient medical records were available for review, which allowed us to abstract pneumococcal vaccination data and other key clinical data. Lastly, our study was performed over a 13-year period in a stable population using consistent data abstraction methods.

Our study also has several potential limitations. First, pneumococcal serotype data were only available from 2002–2007, which limited our ability to make conclusions about shifts in

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serotype distributions prior to introduction of PCV-7 in 2000. Second, there were isolates with unknown serotypes from 2002–2004; however, due to the small number of these, study conclusions were not greatly impacted. Lastly, the Olmsted County population is largely white and our findings should only be generalized to similar populations.

In conclusion, we observed a recent increase in the incidence of IPD in Olmsted County, Minnesota, mainly due to non PCV-7 serotypes. These findings are unique and merit further monitoring to observe for “replacement disease” due to non PCV-7 serotypes in adults.

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Table 1

Temporal trends in incidence rates of invasive pneumococcal disease in Olmsted County, Minnesota in patients aged ≥ 50 years

	IPD incidence rate* (cases per 100,000 person-years)			p value		
IPD incidence rates	**1995–1999**	**2001–2003**	**2004–2007**	**1995–1999 vs 2001–2003**	**2001–2003 vs 2004–2007**	**1995–1999 vs 2004–2007**
Overall IPD incidence rate	24.5	17.7	32.1	NS†	0.029	NS
IPD incidence by gender						
Male	26.5	23.1	34	NS	NS	NS
Female	22.9	13.3	30.6	NS	0.038	NS
IPD incidence by clinical syndrome						
Invasive pneumonia	23.8	14.6	27.8	NS	0.030	NS
Bacteremia without a focus	0.7	1	1.5	NS	NS	NS
Meningitis	0	1	0.7	NS	NS	NS
Other syndromes‡	0	1	2.2	NS	NS	NS
IPD incidence by penicillin susceptibility						
Susceptible	17.5	15.6	25.6	NS	NS	NS
Non-susceptible	4.9	2.1	5.8	NS	NS	NS
Unknown	2.1	0	0.7	NS	NS	NS

*IPD = invasive pneumococcal disease. Incidence rates are sex-adjusted to the US white 2000 population.

†NS = not significant (i.e. p value ≥0.05).

‡Other syndromes included prosthetic and native joint septic arthritis and purulent otitis media.

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Table 2

Temporal trends in incidence rates of invasive pneumococcal disease in Olmsted County, Minnesota in patients aged ≥ 50 years, stratified by serotype

	IPD incidence rate* (cases per 100,000 person-years)		p value†
IPD incidence rates	**2002–2004**	**2005–2007**	
IPD due to non PCV-7 serotypes‡	9.2	32.8	<0.001
IPD due to PCV-7 serotypes	4.1	2.9	0.654
IPD due to unknown serotypes	5.1	0	0.040

*IPD = invasive pneumococcal disease. Incidence rates are sex-adjusted to the US white 2000 population.

†p value compares rates from 2002–2004 to 2005–2007.

‡PCV-7 = 7-valent pneumococcal conjugate vaccine.

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Table 3

Temporal trends in invasive pneumococcal disease cases in Olmsted County, Minnesota in patients aged ≥ 50 years, stratified by serotype (n=55)

	Number of isolates	
Pneumococcal serotype	**2002–2004 (n=18)**	**2005–2007 (n=37)**
PCV-7*		
4	3	1
9V	1	0
6B	0	1
19F	0	1
PCV-7 related		
19A	1	5
6A	2	4
9N	0	3
23A	0	2
23-valent†		
22F	0	2
3	1	5
8	1	2
33F	1	2
11A	0	1
20	1	0
1	0	1
Non-vaccine		
35F	0	3
7C	1	1
15A	0	2
35B	1	0
31	0	1
Unknown	5	0

*PCV-7 = 7-valent pneumococcal conjugate vaccine serotype.

†23-valent = 23-valent pneumococcal polysaccharide vaccine serotype.