The Changing Epidemiology of Invasive Pneumococcal Disease at a Tertiary Children's Hospital Through the 7-valent Pneumococcal Conjugate Vaccine Era

A Case for Continuous Surveillance

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Background: In 2000, a 7-valent pneumococcal conjugate vaccine (PCV7) was licensed for use among US children. Many sites have since reported changes in invasive pneumococcal disease (IPD). We recognized an opportunity to describe the changes in epidemiology, clinical syndromes, and serotype distribution during a 14-year period including 4 years before vaccine introduction and spanning the entire PCV7 era.

Methods: Cases were defined as children <18 years of age who were cared for at Primary Children's Medical Center for culture-confirmed IPD. We defined the prevaccine period as the time frame spanning from 1997 to 2000 and the postvaccine period from 2001 to 2010. Demographics, clinical data, and outcomes were collected through electronic query and chart review. *Streptococcus pneumoniae* serotyping was performed using the capsular swelling method.

Results: The median age of children with IPD increased from 19 months during the prevaccine period to 27 months during postvaccine period ($P = 0.02$), with a larger proportion of IPD among children older than 5 years. The proportion of IPD associated with pneumonia increased substantially from 29% to 50% ($P < 0.001$). This increase was primarily attributable to an increase in complicated pneumonia (17% to 33%, $P < 0.001$). Nonvaccine serotypes 7F, 19A, 22F, and 3 emerged as the dominant serotypes in the postvaccine period. In children with IPD who were younger than 5 years, for whom vaccine is recommended, 67% of the cases were caused by serotypes in 13-valent PCV during 2005 to 2010.

Conclusions: After PCV7 was introduced, significant changes in IPD were noted. One-third of IPD occurred in children older than 5 years, who were outside the age-group for which PCV is recommended. Continued surveillance is warranted to identify further evolution of the epidemiology, clinical syndromes, and serotype distribution of *S. pneumoniae* after 13-valent PCV licensure.

Key Words: *Streptococcus pneumoniae*, invasive pneumococcal disease, serotype, PCV7, PCV13

(*Pediatr Infect Dis J* 2012;31: 228–234)

In 2000, a 7-valent pneumococcal conjugate vaccine (PCV7 [Prevnar]; Wyeth Lederle Vaccine) was licensed for use in young children in the United States. With increasing use of PCV7 in the United States,[1] the epidemiology of invasive pneumococcal disease (IPD) has changed significantly. The Centers for Disease Control and Prevention (CDC) active bacterial core (ABC) surveillance sites report the incidence of IPD in children younger than 5 years decreased more than 70% from 95 cases/100,000 individuals in 1999 to 23 cases/100,000 individuals in 2004.[2] However, these changes have been heterogeneous, with some centers in the United States and other regions of the world reporting less dramatic decreases and the early emergence of IPD caused by non-PCV7 serotypes.[2–7] The causes of the heterogeneous impact of PCV7 remain unknown.

To further protect children against IPD, including IPD caused by emerging *Streptococcus pneumoniae* serotypes, a 13-valent pneumococcal conjugate vaccine (PCV13; Wyeth/Pfizer Pharmaceuticals Inc.), with antigens representing 6 of the serotypes that emerged after licensure of PCV7, was licensed for use in children in the United States in February 2010.[8] The objective of this study was to review the epidemiology and serotypes of culture-confirmed IPD in hospitalized children using laboratory-based surveillance at Primary Children's Medical Center, in Salt Lake City, Utah, from the pre-PCV7 period to the eve of the introduction of PCV13.

METHODS

Human Subject Protection

The institutional review boards of the University of Utah, PCMC, and Intermountain Healthcare (Intermountain) approved this study with a waiver of informed consent.

Setting and Study Population

PCMC, an Intermountain hospital, is the only children's hospital in the intermountain west region of the United States. In addition to Utah, PCMC receives referrals from Idaho, Wyoming, Nevada, and Montana. PCMC also serves as a community pediatric hospital for Salt Lake County, Utah. During the study period,

Accepted for publication October 18, 2011.

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Supported by grants from the National Institute of Allergy and Infectious Diseases (U01A1082482) (to K.A., C.L.B.), (U01 AI074419-01) (to C.L.B., A.J.B., A.T.P.), (U01AI082184-01) (to A.T.P., A.J.B.), 1K23-AI079401-01A1 (to A.J.B.); National Institute of Child Health and Human Development (K-24 HD047249-01A1) (to C.L.B.); and the Centers for Disease Control Prevention (U18-IP000303-01) (to K.A., C.L.B., A.T.P., A.J.B.). This project was further supported by the University of Utah, Department of Pediatrics through the Children's Health Research Center and the Pediatric Clinical and Translational Research Scholars Program, the H. A. and Edna Benning Presidential Endowment, and the Primary Children's Medical Center Foundation. The authors have no other funding or conflicts of interest to disclose.

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ISSN: 0891-3668/12/3103-0228
DOI: 10.1097/INF.0b013e31823dcc72

hospital admissions to PCMC increased from 6418 in 1997 to 9824 in 2010, with a peak of 10,268 in 2009 associated with the H1N1 pandemic. During the study period, the catchment area for PCMC did not change, although the population of the intermountain west increased significantly.

The study period spanned from January 1997 to December 2010. We defined 3 time periods for analysis based on levels of PCV7 coverage. The prevaccine period was the 48-month period from January 1997 to December 2000, preceding PCV7 licensure in the U.S. We defined the early vaccine period as the 48 months from January 2001 to December 2004, when PCV7 uptake (≥3 doses) was increasing but coverage was less than 80% for children younger than 36 months. The late vaccine period included the 72 months from January 2005 to December 2010 when PCV7 coverage was greater than 80% for children in Utah. For some analyses, we combined the period during 2001 to 2010 as the postvaccine period. Vaccine coverage rates for PCV7 in Utah as determined by the National Immunization Survey were similar to those reported nationally.[1] Immunization status was assessed on the basis of the CDC's Advisory Committee on Immunization Practices recommendations.[9]

Identification of Culture-confirmed *S. pneumoniae* Infection

Culture-confirmed IPD cases were defined as children younger than 18 years with *S. pneumoniae* isolated from a normally sterile site (eg, blood; cerebrospinal fluid; joint, pleural, or peritoneal fluid; or abscess). PCMC laboratory staff had archived all pneumococcal isolates from children with IPD since 1996. *S. pneumoniae* serotyping was performed at Baylor College of Medicine (Edward O. Mason) using the capsular swelling method as previously described.[3] Demographic and clinical information, chronic medical conditions predisposing to IPD, and antimicrobial susceptibilities of IPD isolates were abstracted from electronic medical records using Intermountain's Enterprise Data Warehouse.

In 2008, the Clinical and Laboratory Standards Institute (CLSI formerly National Committee for Clinical Laboratory Standards) published new breakpoints for parenteral penicillin therapy for *S. pneumoniae* from nonmeningeal and meningeal sites.[10] For this study and similar to a previous study,[11] all *S. pneumoniae* penicillin and cefotaxime breakpoints used were those for parenteral nonmeningeal infections regardless of the site of isolation. Thus, we defined isolates as penicillin susceptible if the minimum inhibitory concentration (MIC) was ≤2.0 μg/mL and cefotaxime susceptible if the MIC was ≤1 μg/mL.[10] From 1997 to 2003, antimicrobial susceptibility to penicillin and cefotaxime was determined using the Kirby-Bauer disk diffusion method (AB Biodisk, Solna, Sweden). Susceptibility testing was performed by the epsilometric test (E-test) during 2004 to 2007 and by the MICroSTREP microtiter method (Seimens Healthcare Diagnostics, West Sacramento, CA) since 2008.

Statistical Analyses

Descriptive statistics were used to summarize the demographic and clinical characteristics of cases. Rates and proportions were compared using χ^2 or Fisher exact tests as appropriate. The Mann-Whitney *U* test was used to perform pairwise comparisons of continuous variables. All reported *P* values are 2-sided. Statistical analyses were performed using Stata 11.2 (StataCorp LP, College Station, TX).

RESULTS

Demographics and Underlying Medical Conditions

During the study period, 513 children with culture-confirmed IPD who were cared for at PCMC were identified. Male patients were overrepresented in both the prevaccine and vaccine periods (59% and 60%, respectively). The median age of children with IPD increased from 19 months during the prevaccine era to 27 months during the postvaccine era ($P = 0.02$). In the prevaccine era, the majority of children with IPD (54%) were younger than 2 years, 27% were between 2 and 4 years, and 20% were older than 5 years. The proportion of children younger than 2 years and with IPD decreased after PCV7 introduction (54% vs. 43%, $P = 0.03$), and the proportion of disease among children aged 5 years or older increased (20% vs. 28%, $P = 0.06$) (Table 1).

There was an increase in the proportion of children with IPD who had one or more underlying chronic medical conditions (1.6% during the prevaccine period vs. 7.5% in the vaccine period, $P = 0.01$). The most common chronic medical condition was cardiac disease (n = 13), followed by neuromuscular disorders (n = 10). Immune-compromising conditions were noted more frequently in the vaccine era (14.5% vs. 5.5%, $P < 0.01$).

Of 385 children with IPD during the vaccine period, immunization records were available for 338 (88%). Of these, 163 (48%) received ≥1 dose of PCV7. As per Advisory Committee on Immunization Practices recommendations, 96 (28%) children were fully immunized with PCV7. After approval of PCV13 in February of 2010, 35 children developed IPD and 33 (94%) had vaccine records available for review. Before hospital admission, 2 (6%) children received ≥1 dose of PCV13.

Outcomes and Antimicrobial Susceptibilities of Culture-confirmed IPD

Outcomes among children with IPD were similar in the prevaccine and vaccine periods. Similar proportions were admitted to the intensive care unit (ICU) (41% in prevaccine period vs. 35% in vaccine period, $P = 0.3$), and the case-fatality rate (4.5%) was similar during the prevaccine and vaccine periods. However, among children 2 years of age and older, the proportion requiring intensive care admission declined from 44% in the prevaccine period to 30% in the vaccine period ($P = 0.04$).

The proportion of *S. pneumoniae* isolates not susceptible to penicillin and cefotaxime decreased during the study period (Table 1), with the highest rates among serotypes 19A (penicillin 64% and cefotaxime 24%).

Clinical Syndromes of IPD

The distribution of clinical syndromes associated with IPD changed substantially by the study period (Fig. 1). In the prevaccine era, bacteremia without focus (37%) was the most frequent cause of IPD, whereas complicated pneumonia (33%) was most frequent during the vaccine period. The proportion of cases attributable to bacteremia without focus declined from 47/128 (37%) in the prevaccine period to 95/385 (25%) in the vaccine period ($P = 0.02$). The proportion attributable to meningitis and musculoskeletal disease remained stable across the 2 study periods. The proportion of IPD associated with pneumonia increased significantly from 37/128 (29%) to 191/385 (50%) ($P < 0.001$). This increase was primarily attributable to an increase in complicated pneumonia (pneumonia complicated by parapneumonic effusion, empyema, necrotizing lung, or lung abscesses). Between the prevaccine period and the vaccine period, the proportion of all IPD attributable to complicated pneumonia increased from 22/128 (17%) to 127/385 (33%) ($P < 0.001$) (Table 1).

TABLE 1. Clinical Characteristics of Invasive Pneumococcal Disease by Serotype Before (1997–2000) and After (2001–2010) Introduction of PCV7

Variable	1997–2000		2001–2010							
	All Serotypes (N = 128)	PCV7 (n = 75)	All Serotypes (N = 385)	PCV7 (n = 58)	7F (n = 72)	19A (n = 62)	1 (n = 29)	3 (n = 28)	22F (n = 23)	Other (n = 113)
Age, n (%)										
<2 y	69 (54)	42 (56)	165 (43)	25 (43)	37 (51)	25 (40)	6 (21)	11 (39)	6 (26)	56 (50)
2–4 y	34 (27)	20 (27)	113 (29)	17 (29)	12 (17)	23 (37)	13 (45)	10 (36)	7 (30)	32 (28)
5–17 y	25 (20)	13 (17)	107 (28)	16 (28)	23 (32)	14 (23)	10 (35)	7 (25)	10 (44)	28 (25)
Clinical syndrome, n (%)										
Meningitis	22 (17)	14 (19)	49 (12)	11 (19)	10 (14)	4 (7)	0	2 (7)	5 (22)	17 (15)
Bacteremia	47 (37)	33 (44)	95 (25)	22 (38)	16 (22)	14 (23)	0	2 (7)	6 (26)	35 (31)
All pneumonia	37 (29)	17 (23)	191 (50)	18 (31)	38 (53)	34 (55)	27 (93)	23 (82)	10 (44)	44 (39)
Uncomplicated	15 (12)	8 (11)	64 (17)	11 (19)	14 (19)	12 (19)	2 (7)	2 (7)	5 (22)	19 (17)
Complicated	22 (17)	9 (12)	127 (33)	7 (12)	24 (33)	22 (36)	25 (86)	21 (75)	5 (22)	25 (22)
Musculoskeletal	10 (8)	5 (7)	30 (8)	6 (10)	6 (8)	7 (11)	0	0	1 (4)	10 (9)
Other	12 (9)	6 (8)	20 (5)	1 (2)	2 (3)	12 (19)	2 (7)	1 (4)	1 (4)	10 (9)
Complication, n (%)										
Admission to intensive care unit	53 (41)	29 (39)	131 (35)	21 (36)	18 (25)	16 (26)	10 (35)	15 (54)	7 (30)	45 (40)
Death	6 (5)	4 (5)	17 (5)	2 (3)	1 (1)	3 (5)	1 (3)	0	0	10 (9)
Antibiotic susceptibility, n (%)										
Penicillin	84 (66)	44 (59)	286 (76)	40 (69)	62 (86)	22 (36)	28 (97)	28 (100)	22 (96)	86 (76)
Cefotaxime	84 (66)	44 (59)	341 (90)	51 (88)	69 (96)	47 (76)	28 (97)	26 (93)	21 (91)	100 (89)

PCV7 indicates 7-valent pneumococcal conjugate vaccine.

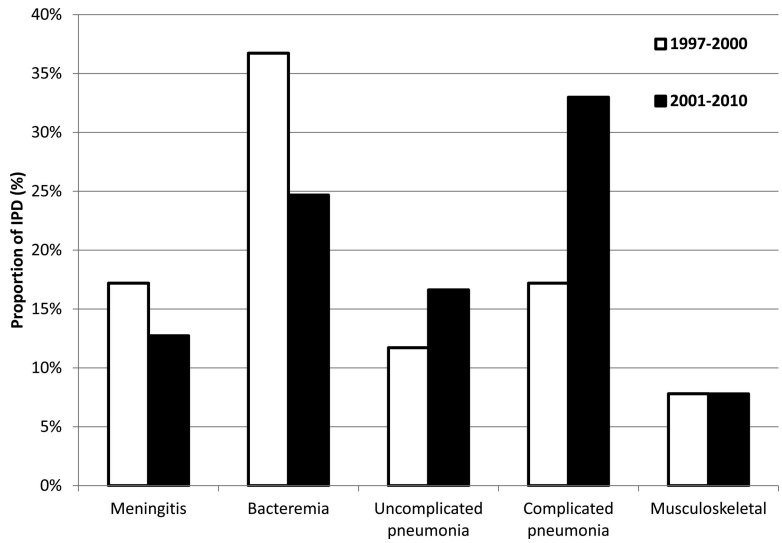

FIGURE 1. Proportion of IPD attributed to clinical syndromes in Utah during the pre- (1997–2000) and postvaccine (2001–2010) periods.

Children with meningitis were significantly younger (median age, 9 vs. 25 months; $P < 0.001$) than other children with IPD, and those with complicated pneumonia were significantly older during both study periods (median age, 37 vs. 25 months; $P < 0.001$). The median age of children with IPD and uncomplicated pneumonia increased from 15 months in the prevaccine period to 31 months during the vaccine period ($P = 0.07$).

Distribution of *S. pneumoniae* Serotypes

The distribution of *S. pneumoniae* serotypes causing IPD in Utah changed significantly between the prevaccine and vaccine periods. The proportion of IPD caused by PCV7 serotypes declined dramatically and continued to decline after introduction of PCV7 in 2000 (59% vs. 15%, $P < 0.001$) (Fig. 2). Between 2001 and 2010, the proportion of disease caused by non-PCV7 serotypes increased significantly (41% vs. 85%, $P < 0.001$). The increase was driven initially by the emergence of serotypes 3 and 19A followed by increases in serotypes 7F, 19A, 22F, and 3 during the late vaccine period (2005–2010) (Fig. 3).

Serotype 7F was the most frequent cause of IPD during the vaccine period, accounting for 72/385 cases (19%), followed by serotype 19A (62/385 isolates [16%]). These predominantly increased between 2005 and 2010 (Fig. 3). More than half of serotype 7F (38/72

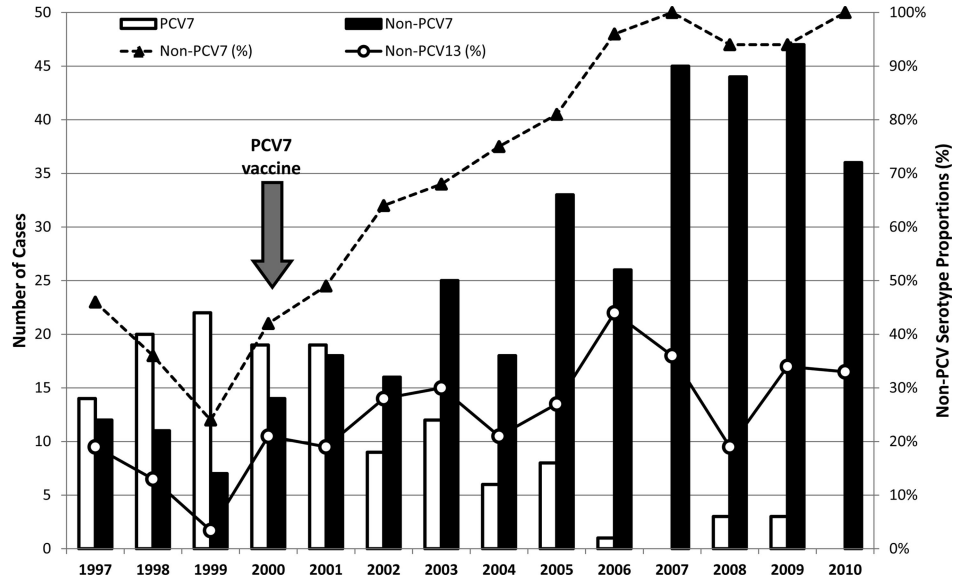

FIGURE 2. Number and proportion (%) of PCV versus non-PCV *S. pneumoniae* in children with culture-confirmed IPD at PCMC, Utah, 1997–2000.

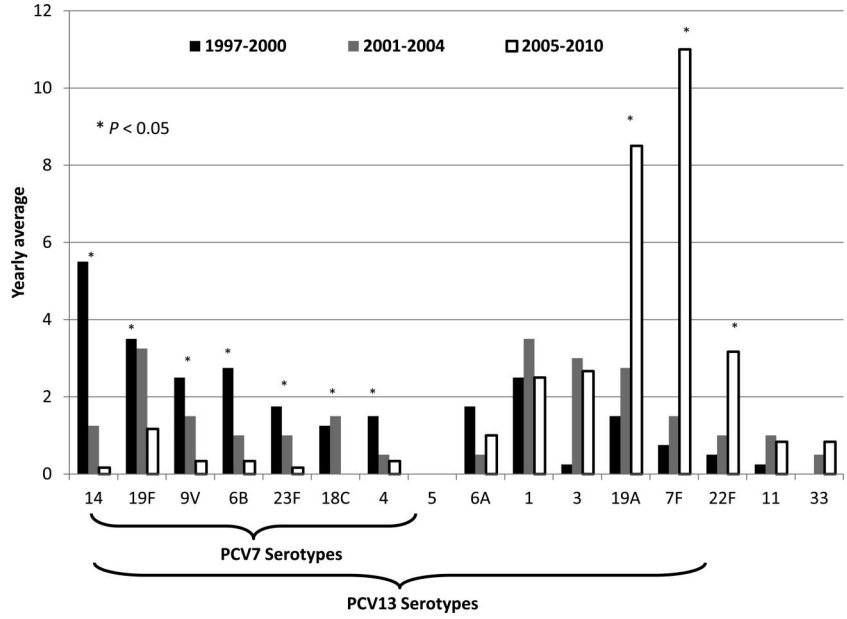

FIGURE 3. Yearly average of *S. pneumoniae* serotypes isolated by PCV7 period among hospitalized children at PCMC, 1997–2010.

[53%]) isolates were from patients with pneumonia (Table 1). Of 72 children with infection caused by serotype 7F, 18 (25%) required ICU admission, but death was infrequent (1%). Fifty-one percent of serotype 7F isolates were from children younger than 2 years compared with 41% of other serotypes ($P = 0.1$) (Table 1).

The majority (55%) of the cases of IPD caused by serotype 19A were associated with pneumonia. Rates of ICU admission (26%) and death (5%) associated with serotype 19A were not different from those of other serotypes (Table 1).

Serotype 3 increased rapidly in the early vaccine period and remained stable thereafter (Fig. 3). Seventy-five percent of all serotype 3 infections were associated with complicated pneumonia. Patients with infections caused by serotype 3 were more likely to be admitted to ICU than patients with infections caused by other serotypes during the postvaccine era ($P = 0.04$) (Table 1).

Serotype 22F, a serotype not included in PCV13, increased during the late vaccine period. Almost 22% of 22F isolates were from patients with meningitis compared with 12% of all other isolates ($P < 0.001$).

Serotype 1, a relatively common serotype among Utah children before licensure of PCV7, remained stable over time (Fig. 3). During the vaccine period, children with serotype 1 infection were

older than children with infection caused by other serotypes (median age, 48 vs. 27 months; $P = 0.04$). The majority of cases of IPD caused by serotype 1 were pneumonia (93%). Serotype 1 was also strongly associated with complicated pneumonia when compared with other serotypes (86% vs. 29%; odds ratio, 14.0; $P < 0.001$) (Table 1).

During the vaccine period, clinical syndromes of IPD varied by serotype and outcome (Table 1). Cases of complicated pneumonia were predominantly caused by *S. pneumoniae* serotype 1 (20%) and emerging serotypes 7F (19%), 19A (17%), and 3 (17%). Meningitis was frequently associated with serotypes 22F and 7F. Of 49 meningitis cases, 39 (80%) required ICU admission and 12% died. Penicillin and cefotaxime nonsusceptibility were highest among meningitis cases (24% and 29%, respectively).

From 2005 to 2010, 67% of all IPD patients cared for at PCMC had infections caused by pneumococcal serotypes contained in PCV13 (Fig. 3). The proportion was similar (67%) in children younger than 5 years, the target group for PCV13. A total of 53% of meningitis, 60% of bacteremia without focus, 64% of uncomplicated pneumonia, and 80% of complicated pneumonia isolates during the late vaccine period (2005–2010) were PCV13 serotypes.

DISCUSSION

We evaluated changes in *S. pneumoniae* serotypes and clinical syndromes in children with IPD at a children's hospital in Utah, spanning 4 years before and 10 years after licensure of PCV7. After the introduction and widespread use of PCV7 in Utah, we observed a shift in culture-confirmed IPD to older children, with an increase in the median age from 18 months to 27 months. The shift was primarily because of a decrease in IPD among children younger than 2 years and an increase among children older than 5 years. There has been a differential effect of PCV7 on the clinical syndromes associated with IPD. Bacteremia without focus declined, whereas complicated pneumonia increased substantially. Invasive infection caused by PCV7 serotypes was virtually eliminated, offset by an increase in emerging non-PCV7 serotypes, especially serotypes 7F, 19A, 22F, and 3. Nonsusceptibility to penicillin and cefotaxime decreased rapidly, and remains lower, despite the emergence of resistant strains of serotype 19A.

Since the introduction of PCV7, studies in a variety of settings have shown a decrease in IPD in all age-groups.[12,13] The largest declines in IPD were among the vaccine target group (<5 years of age) and in adults and the elderly, presumably as a result of herd immunity.[4,12,14] Similarly, we recently reported significant declines in the incidence of IPD in Utah children aged <2 years and 2 to <5 years, with no change among those aged 5 to 17 years.[15] It is of note that the emergence of non-PCV7 serotypes has been associated with a shift to a greater proportion of IPD occurring in older children. We observed increases in the age of children with bacteremia without focus and pneumonia (both complicated and uncomplicated). Chibuk et al noted a similar increase in the age of children with complicated pneumonia in Canada.[16] In contrast, Li and Tancredi, using US hospital discharge data, reported a decrease in the age of children hospitalized with empyema from 7.3 years to 6.3 years between 1997 and 2006.[17] These findings have implications for identifying the optimal age for use of PCV13. It will be critical to determine if using the vaccine exclusively in children younger than 5 years will translate into a decrease in IPD in older children.

We observed an increase in the proportion of children with underlying chronic medical conditions from 1.6% in the prevaccine period to 7.5% during the vaccine period. Our findings are supported by results from a case-control study evaluating the effectiveness of PCV7 against IPD, using data from the CDC's ABC surveillance sites.[18] Among healthy children, the effectiveness of ≥1 dose of PCV7 against vaccine serotypes was 96% (95% confidence interval [CI], 93–98), whereas among children with chronic medical conditions, PCV7 vaccine effectiveness was significantly lower at 81% (95% CI, 57–92) ($P = 0.001$). In another study, Park et al demonstrated that IPD caused by vaccine serotypes occurred 2.8 times more frequently among children with an identified chronic medical condition, when compared with IPD caused by nonvaccine serotypes (95% CI, 1.3–6.1) among children who had received ≥1 dose of PCV7.[19] Together, these data support the finding that PCV7 is less effective among children with chronic medical conditions. In our study, the proportion of immune-compromising conditions increased 3-fold by the vaccine period. A report from South Africa demonstrated decreased efficacy of the 9-valent pneumococcal conjugate vaccine among HIV-infected children,[20] and it is likely that among children with congenital and acquired immunodeficiency syndromes, protective immunity after PCV7 vaccination is lower than among healthy children.

The epidemiology of IPD varies significantly by geographic region.[21] Ongoing surveillance of IPD at the CDC's ABC sites until 2007 noted increases in infection caused by non-PCV7 serotypes in all sites, with significant increases in serotypes 19A, 15, 33F, 22F, 3, and 5.[2,21,22] In Massachusetts, infections caused by serotype 19A increased from 10% of IPD in 2002 to 41% in 2006.[23] In our study, serotypes 7F, 19A, 3, and 22F have increased and collectively account for 49% of IPD in the vaccine period. The largest increase was in serotype 7F, which predominantly emerged in the later years of the study. After 2005, serotype 7F has been the leading cause of bacteremia without focus, meningitis, and both uncomplicated and complicated pneumonia. Serotype 19A emerged in the early vaccine period. In many regions of the United States, serotype 19A has become the most common serotype causing IPD since the licensure of PCV7.[2,11,24–26] However, in our population, serotype 7F has surpassed 19A and accounted for 20% of meningitis cases. Serotype 22F, a serotype not included in PCV13, increased considerably in the late vaccine period and represented 6% of all IPD and 10% of meningitis. Other recent studies have reported the increasing role of serotype 22F in meningitis.[22,27] In our study, serotypes 1 (86%) and 3 (75%) were strongly associated with complicated pneumonia, consistent with previous reports.[5,28–31]

The recently licensed PCV13 targets several of the common nonvaccine serotypes that have emerged in the United States. By the late vaccine period (2005–2010), 64% of isolates from children <18 years of age and 59% of isolates from children <5 years of age in our study were serotypes contained in PCV13. Our findings are similar to those of Pilishvili et al, who report that 68% of IPD among children <5 years of age in the ABC sites during the 2006–2007 season was caused by PCV13 serotypes.[32] Interestingly, when specific clinical syndromes were evaluated, the proportion of disease caused by PCV13 serotypes varied significantly. PCV13 serotypes were responsible for 85% of complicated pneumonia but only 55% of meningitis from the late vaccine period (2005–2010). Thus, the introduction of PCV13 may affect specific IPD clinical syndromes differently.[8]

The widespread use of PCV7 was associated with a significant decrease in the proportion of penicillin and cefotaxime nonsusceptible *S. pneumoniae*, in agreement with previous reports.[2–4,12,22,33] Reductions in nasopharyngeal colonization of penicillin-nonsusceptible PCV7 isolates previously associated with IPD, and colonization by non-PCV7 serotypes, which have generally been susceptible, likely contributed to the overall in-

crease in susceptibility of *S. pneumoniae* to penicillin and cefotaxime.[34,35] Decreases in antibiotic prescribing for outpatients with upper respiratory tract infections may be another factor.[35] However, the emergence of multidrug-resistant clones of serotype 19A poses a threat to these gains in Utah and other regions.[25,36–38] A mathematical model predicted the development of resistance in emerging *S. pneumoniae* serotypes with sustained antibiotic use that could reverse the gains of PCV7.[39] Thus, vaccine use must be coupled with more prudent use of antibiotics to control antimicrobial resistance among *S. pneumoniae*.

This study has a number of limitations. First, it is based in a single geographic area, and pneumococcal epidemiology is known to have substantial regional variation. However, our findings are generally in accordance with reports from other parts of North America and Europe.[2,4,12] Second, vaccination records were available for a majority of children with IPD (88%); however, they were not available for all children. Lastly, like many other studies, serotyping was only performed on patients with viable isolates, which represent a modest proportion of all patients with IPD. Antibiotic pretreatment, the low rate of bacteremia in pneumococcal pneumonia, and the tendency of *S. pneumoniae* for autolysis limit the recovery and may bias the serotype distribution. We have demonstrated differences in serotype distribution in pleural fluid samples when molecular methods are employed, and future surveillance studies may produce a more complete picture of serotype distribution in IPD if molecular methods can be employed in addition to culture.[40]

In summary, PCV7 vaccination has had a differential effect on *S. pneumoniae* serotype distributions, age distribution, clinical syndromes, and antibiotic susceptibilities in Utah. After vaccine introduction, children with IPD in Utah were older. Up to a third of IPD occurred in children older than 5 years, outside the age-group for which PCV is recommended. Non-PCV7 serotypes 7F, 19A, 22F, 3, and 1 have emerged as the dominant serotypes, and complicated pneumonia has increased. At the time of licensure of PCV13, ~70% of IPD was caused by serotypes in PCV13. The changes in *S. pneumoniae* epidemiology in children and adults after the introduction of PCV7 have been complex and not completely understood. Similar complex changes are likely to evolve as PCV13 coverage increases. Continued surveillance is essential to identify further evolution of the epidemiology, clinical syndromes, and distribution of serotypes of invasive *S. pneumoniae* disease to optimize prevention strategies.

ACKNOWLEDGMENTS

The authors thank PCMC Microbiology Laboratory for storing and archiving S. pneumoniae *isolates and Intermountain Healthcare, Salt Lake City, Utah.*

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