Early Trends for Invasive Pneumococcal Infections in Children Following the Introduction of the 13-Valent Pneumococcal Vaccine

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ABSTRACT

Background: Invasive pneumococcal infections (IPI) in children were reduced about 75% following the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7). Since 2005 IPI in children have increased due to non-PCV7 serotypes, especially 19A. In February 2010, PCV13 (PCV7 + serotypes 1, 3, 5, 6A, 7F and 19A) was approved and we report the early experience with IPI in children since then.

Method: Children with IPI have been prospectively identified by investigators from 8 children's hospitals in the United States since 1993. Demographic and clinical data are collected on case report forms and isolates are sent to a central laboratory where the serotyping and antibiotic susceptibilities are performed. The % of isolates with penicillin MICs > 2 µg/mL is reported. Data were analyzed for 12 month periods starting July 1, 2007 through June 30, 2011. Dichotomous variables were analyzed by Chi-square.

Results: The total number of IPI cases, number of serotype 19A, 7F, 3 and 6C isolates and the % of children < 60 mo for each of the study years are shown in the table. In 2010-11 serogroup 15 (n=9; 15A-2, 15B-3, 15C-4) was also common. Isolates with penicillin MIC > 2 µg/mL decreased significantly over the study years (p=0.003) In 2010-11, 43% of children had underlying conditions. Among cases in 2010-2011, 42 children had received one (n=27), or more doses (2 doses-9, 3 doses-6) of PCV13; 16 isolates (12 were 19A) were PCV13 serotypes. 6/16 had underlying conditions. Serotype 33F was found in 3/6 who had received 3 PCV13 doses.

Isolates	2007-8	2008-9	2009-10	2010-11
Total	211	209	210	133
19A	85	72	75	43
7F	24	25	33	14
3	14	16	12	8
6C	7	6	10	4
33F	0	0	4	10
%< 60 mo old	72	68	75	61
% MIC > 2µg/mL 8	6	1	0	

Conclusions: Early trends indicate a 36% reduction in IPI cases among 8 children's hospitals for the 12 month period starting 4 months after the introduction of PCV13. Penicillin resistance also decreased. 19A cases were reduced by 45%. Some cross protection for 6C is likely. Serotype 33F and serogroup 15 were the most common non-PCV13 serotypes encountered. Continued surveillance is necessary to further document the impact of PCV13 on IPI in children.

OBJECTIVES

To describe the early trends for invasive pneumococcal infections in children seen at 8 children's hospitals in the United States following the introduction of the 13-valent pneumococcal conjugate vaccine

INTRODUCTION

- *Streptococcus pneumoniae* is an important cause of bacteremia, meningitis, pneumonia and other invasive infections in infants and children.
- The 7-valent pneumococcal conjugate vaccine, PCV7, was introduced in 2000 and protects against serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. It also has protected well against serotype 6A. PCV7 has lead to an approximately 75% reduction in invasive pneumococcal infections (IPI) in children although IPI due to non-PCV7 serotypes increased slightly by 2005, especially for serotype 19A isolates.
- The 13-valent pneumococcal conjugate vaccine, PCV13, adds serotypes 1, 3, 5, 6A, 7F and 19A to the serotypes in PCV7 and was licensed in the United States for routine administration to infants in February 2010.
- Data describing the early trends for IPI following the licensure of PCV13 are of interest.

METHODS

Patients and Isolates

- The United States Pediatric Multicenter Pneumococcal Surveillance Group, consisting of 8 children's hospitals in the US, has prospectively identified children with IPI since 1993.
- Patients with IPI are identified prospectively and their pneumococcal isolates are collected from the respective microbiology laboratories.
- Patient information regarding demographics, co-morbid conditions, dates of receipt of the PCV7 or PCV13 vaccines, and site of *S. pneumoniae* infections was obtained retrospectively and recorded on standardized case report forms (CRF).
- Isolates and CRF were sent to a central laboratory at Texas Children's Hospital. Isolates were serotyped using the Quellung reaction and specific antisera (Statens Serum Institut, Denmark). Antimicrobial susceptibility was determined by microbroth dilution (penicillin and ceftriaxone) or by Kirby Bauer disk diffusion (clindamycin, erythromycin, and trimethoprim-sulfamethoxazole [TMP/SMX]) according to Clinical Laboratory Standards Institute (CLSI) guidelines.
- Data were analyzed for 12 month periods; Period 1: 7/1/07 to 6/30/08; Period 2: 7/1/08 to 6/30/09; Period 3: 7/1/09 to 6/30/10; Period 4: 7/1/10 to 6/30/11

Statistical Analysis

- Chi-square for trend was computed using STATA 10 (College Station, Texas). Analyses were 2-tailed, and a p<0.05 was considered statistically significant.
- The study was approved by the Institutional Review Boards of each institution.

Table 1. Number of Isolates for All Serotypes , the Most Common Serotypes and Added PCV13 Serotypes for the 12 Month Periods -July 1 to June 30

Serotype	2007-8	2008-9	2009-10	2010-11
All	211	209	210	133
1	4	7	3	2
3	14	16	12	8
5	0	1	1	0
6A	0	0	1	1
6C	7	6	10	4
7F	24	25	33	14
11	3	2	0	5
15A	3	1	2	2
15B	5	5	6	3
15C	5	4	2	4
19A	85	72	75	43
22F	4	10	11	2
23A	4	2	3	6
23B	5	6	3	5
33A	5	3	1	0
33F	0	0	4	10

RESULTS

- The total number of IPI cases, isolates of the serotypes added to PCV13 (1, 3, 5, 6A, 7F, 19A), and isolates of the most common non-PCV13 serotypes are shown in Table 1 for each of the 12 month study periods from July 1, 2007 through June 30, 2011.
- The total IPI cases in 2010-11 decreased 36% compared to the prior 12 month periods.
- 19A isolates decreased by 45% in 2010-11 compared to the prior 12 month periods.
- Serotype 3 and 7F isolates also diminished in the 2010-11 period compared to the prior 3 periods.
- Only two isolates each were noted for serotype 5 and 6A over the entire study period. For serotype 6C , the lowest number of isolates occurred in period 4.
- For serotype 33F, no isolates were found in the first 2 periods compared with 4 and 10 isolates for periods 3 and 4, respectively.
- Serogroup 15 and serotypes 23A/B and serotype 11 isolates also increased during the study period.
- Over the 4 year period the numbers of isolates with PCV7 serotypes were: **4**-3, **6B**-2, **9V**-2, **14**-4, **18C**-3, **19F**-10 and **23F**-1.
- The percentages of children who were < 60 months old were 72%, 68%, 75%, and 61% for periods 1, 2, 3, and 4, respectively.
- The percentages for children who were < 24 months old were 49%, 44%, 48%, and 35% for periods 1, 2, 3 and 4, respectively.
- The percentages of children with underlying conditions were 39%, 35%, 40% and 43% for periods 1, 2, 3, and 4, respectively. Malignancy, cardiovascular and central nervous system disorders were the most common underlying conditions in all study periods.
- The sites of infection for the study periods are shown below (Table 2). Only the number of meningitis cases did not decline for 2010-11 compared with previous periods.

Table 2. Sites of infection, 2007-2011

Site	2007-8	2008-9	2009-10	2010-11
Bacteremia	83	68	78	52
Pneumonia	59	75	67	34
Meningitis	28	26	26	24
Mastoiditis	19	20	16	3

Prior Pneumococcal Conjugate Vaccine Administration

- In 2010-2011, 42 children had received one or more doses of PCV13 at least 2 weeks prior to the development of IPI.

One dose 27 children, 10 with isolates having PCV13 serotypes (**19A**-7, **3**-2, **7F**-1). 4 children with 19A had underlying conditions. **33F**, serogroup **15**, and serogroup 23 accounted for 3 isolates each.

Two doses 9 children, 4 with isolates having PCV13 serotypes (**19A**-4). One patient with 19A had hydronephrosis and one had a branchial cleft cyst. Two isolates were serotype 15B.

Three doses 6 children, 1 isolate having a PCV13 serotype (**19A**). **33F** accounted for 3 isolates and **15A** for one isolate. One isolate could not be typed.

Antimicrobial Susceptibility

- The distribution of penicillin MICs for pneumococcal isolates from IPI in the 4 study periods is shown in **Figure**. The number of isolates with penicillin MICs ≥ 4 µg/mL decreased steadily over the study periods and by 2010-2011 there were no isolates with MICs in this category (p <0.001). All isolates in 2010-2011 with penicillin MICs = 2 µg/mL were serotype 19A. A similar decrease was seen for isolates with ceftriaxone MICs ≥ 4 µg/mL .
- The percentage of isolates resistant to erythromycin, clindamycin and trimethoprim-sulfamethoxazole did not change over the study periods. (**Table 3**)

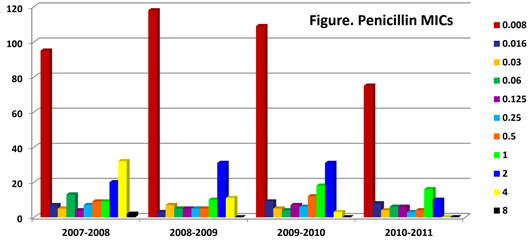

Table 3. Percentage Resistance for Selected Antibiotics

Antibiotic	2007-8	2008-9	2009-10	2010-2011
Erythromycin	36	35	40	37
Clindamycin	27	24	25	23
TMP/SMX	44	38	39	38

CONCLUSIONS

- Invasive infections caused by *S. pneumoniae* in children seen at 8 children's hospital has decreased by 36% following the introduction of PCV13 in the time period July 1, 2010 to June 30, 2011 when compared to the three prior 12 month intervals.
- Invasive pneumococcal infections caused by serotype 19A isolates declined 45% . Infections caused by the five other added PCV13 serotypes also declined.
- Serotype 6C isolates declined in period 4 compared with the previous 3 periods suggesting some cross protection from serotype 6A added to PCV13.
- Serotype 33F, serotype 23A/B and serogroup 15 appear to be on the increase following PCV13 licensure.
- Only six children were identified who had received 3 doses of PCV13 prior to IPI. One had a 19A isolate and 33F was recovered in 3 patients.
- High level resistance to penicillin and ceftriaxone was decreased in 2010-11 and no isolates had penicillin or ceftriaxone MICs ≥ 4 µg/mL . However, the percentage of isolates resistant to erythromycin, clindamycin or TMP/SMX did not change over the study period.
- Continued surveillance of IPI in children is required.

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