MAJOR ARTICLE

Impact of the 13-Valent Pneumococcal Conjugate Vaccine on Pneumococcal Meningitis in US Children

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(See the Editorial Commentary by Ladhani and Ramsay on pages 776–8.)

Background. The impact of 13-valent pneumococcal conjugate vaccine (PCV13) on pneumococcal meningitis (PM) in US children is unknown. We compared the serotype distribution, antibiotic susceptibility, hospital course, and outcomes of children with PM 3 years before and 3 years after the introduction of PCV13.

Methods. We identified patients ≤18 years of age with PM at 8 children's hospitals in the United States. Pneumococcal isolates were collected prospectively. Serotyping and antibiotic susceptibility were performed in a central laboratory. Clinical data were abstracted from medical records. Patients were divided into 3 subgroups: pre-PCV13 (2007–2009), transitional year (2010), and post-PCV13 (2011–2013). Categorical variables were analyzed by the χ^2 test and continuous variables by the Mann–Whitney *U* test.

Results. During the study period, 173 of 1207 episodes (14%) of invasive pneumococcal disease were identified as PM; 76 of 645 (12%) were during 2007–2009 and 69 of 394 (18%) during 2011–2013 (50% increase; $P = .03$). The proportion of PCV13 serotype cases decreased from 54% in 2007–2009 to 27% in 2011–2013 ($P = .001$). Non-PCV13 serotype cases represented 73% of the isolates in 2011–2013. Isolates with ceftriaxone minimum inhibitory concentration ≥1 μg/mL decreased (13% to 3%) from 2007–2009 to 2011–2013 ($P = .03$). No significant differences were identified for hospital course or outcome, with the exception that a greater proportion of patients had subdural empyema and hemiparesis in 2011–2013.

Conclusions. After the introduction of PCV13, the number of cases of PM in children remained unchanged compared with 2007–2009, although the proportion of PCV13 serotypes decreased significantly. Serotype 19A continued to be the most common serotype in 2011–2013. Antibiotic resistance decreased significantly. Morbidity and case-fatality rate due to PM remain substantial.

Keywords. meningitis; *Streptococcus pneumoniae*; conjugate vaccine; pneumococcal disease.

Streptococcus pneumoniae is the leading cause of bacterial meningitis in children outside the neonatal period in the United States [1]. Moreover, among all bacterial meningitides, pneumococcal meningitis (PM) is associated with the highest long-term disability and case-fatality rate (CFR) [2]. In the United States and some European countries, the CFR of PM ranges from 7% to 13% in children; however, outside these areas, the CFR has been reported to be as high as 73% [1, 3–11]. Neurological sequelae occur in 25%–63% of survivors [3, 6, 8, 12].

The introduction of a 7-valent pneumococcal conjugate vaccine (PCV7; serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) in the United States in 2000 had a significant impact on the incidence of invasive pneumococcal disease (IPD)

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and PM among children, particularly children <2 years of age [1, 5, 13–15]. Correspondingly, the average rate of PM hospitalizations among children aged <2 years decreased 66% from 1994–1999 to 2001–2004 [16]. The Active Bacterial Core surveillance (ABCs) network reported a reduction of 62% (from 9.69 to 3.67 cases per 100 000 population) in PM among children aged 2–23 months and an increase of 92% (from 0.87 to 1.67 cases per 100 000 population) in the incidence of PM caused by non-PCV7 serotypes among children aged <5 years from 1998–1999 to 2006–2007, respectively [1].

In 2010, a 13-valent pneumococcal conjugate vaccine (PCV13), which added serotypes 1, 3, 5, 6A, 7F, and 19A to PCV7, was recommended for routine use in US children. The first year after the introduction of PCV13, the overall number of IPD cases decreased 42% compared with 2007–2009 in our surveillance study [17]. We also observed a significant reduction of the number of cases of pneumococcal bacteremia and pneumonia; however, cases of PM remained stable [17]. To our knowledge, no studies to date report the impact of PCV13 on PM in US children. Our objective was to compare changes in the epidemiology of PM 3 years before and 3 years after the introduction of PCV13 among US children, including serotype distribution, antibiotic susceptibility, hospital course, and clinical outcomes.

METHODS

Setting, Population, and Design

The US Pediatric Multicenter Pneumococcal Surveillance Study Group consists of investigators from 8 children's hospitals who have been prospectively identifying children with IPD since September 1993 [14]. We identified patients ≤18 years of age with PM from our database between 1 January 2007 and 31 December 2013. PM was defined as an *S. pneumoniae*–positive cerebrospinal fluid (CSF) culture and/or a positive blood culture with CSF pleocytosis (>10 cells/μL). The study was divided into 3 periods: pre-PCV13 (January 2007–December 2009), PCV13 introduction year (2010), and post-PCV13 (January 2011–December 2013). The study was approved by the institutional review boards of each of the participating hospitals.

Microbiologic Methods

Pneumococcal isolates were identified using standard methods in the microbiology laboratories of each hospital. All isolates were sent to a central laboratory (Infectious Disease Research Laboratory, Texas Children's Hospital, Houston) for serotyping by the capsular swelling method using commercially available antisera (Statens Serum Institut, Copenhagen, Denmark; Dako, Inc, Carpinteria, California) [18]. Determination of minimum inhibitory concentrations (MICs) for penicillin and ceftriaxone was performed by microbroth dilution with Mueller-Hinton media supplemented with 3% lysed horse blood. Susceptibility categories were determined using the 2013 Clinical and Laboratory Standards Institute guidelines (meningitis breakpoints for pneumococci: penicillin, ≤0.06 μg/mL = susceptible and ≥0.12 μg/mL = resistant; ceftriaxone, ≤0.5 μg/mL = susceptible, 1.0 μg/mL =intermediate, and ≥2.0 μg/mL = resistant) [19].

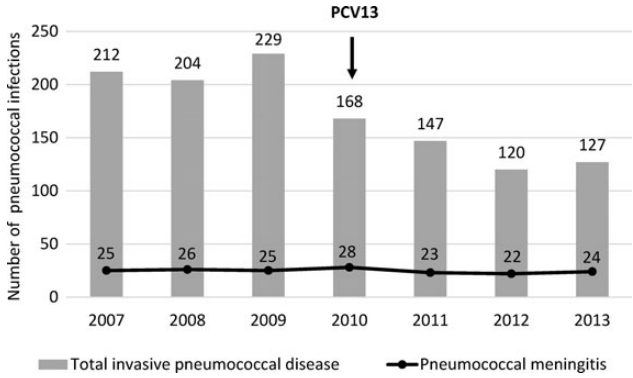

Figure 1. Number of invasive pneumococcal disease and pneumococcal meningitis cases per year among 8 children's hospitals in the United States, 2007–2013. Abbreviation: PCV13, 13-valent pneumococcal conjugate vaccine.

Data Collection and Definitions

Clinical information was abstracted from medical records and recorded on a standardized case report form that included demographics, clinical presentation, laboratory results, neuroimaging findings, management, dexamethasone use, complications, and neurological sequelae. Adequate use of dexamethasone was defined as a minimum of 8 doses administered every 6 hours (0.15 mg/kg/dose) with the first dose administered before or within an hour of antibiotic administration. Authors documented the dates of administration of PCV7/PCV13 through the medical records or by contacting the patient's healthcare provider. Advisory Committee on Immunization Practices recommendations for the use of PCV7 [20, 21] and PCV13 [22] were used to categorize the immunization status of our patients: (1) adequately immunized (patients who received the recommended number of PCV7/PCV13 doses according to age and comorbidity); (2) partially immunized (patients who missed 1 or more doses of PCV7/PCV13); (3) too young to be immunized (patients <2 months of age); and (4) unimmunized (patients who were eligible to receive PCV7/PCV13 but did not receive any doses).

Statistical Analysis

Descriptive statistics were used to characterize the study population. The χ^2 test and Fisher exact test were used to compare categorical variables. Continuous variables were analyzed by the Mann–Whitney *U* test. Associations are presented as odds ratio with 95% confidence intervals. Predictors for sequelae were evaluated using a univariate analysis and a backward stepwise logistic regression model. A 2-tailed *P* value ≤.05 was considered statistically significant. IBM SPSS statistics version 22.0.0 was the statistical program used.

Table 1. Demographic Characteristics, Underlying Conditions, and Immunization Status of Pediatric Patients With Pneumococcal Meningitis

Characteristic	2007–2009 (n = 76)	2010[a,b] (n = 28)	2011–2013 (n = 69)	*P* Value[a]
Sex, male, No. (%)	44 (58)	17 (61)	43 (62)	.6
Race/ethnicity, No. (%)				
White	41 (54)	16 (57)	32 (46)	.4
Black	14 (18)	2 (7)	16 (23)	.5
Hispanic	12 (16)	5 (18)	15 (22)	.4
Other	9 (12)	5 (18)	6 (9)	.6
Age, mo, median (IQR)	15.7 (5.4–70)	12.6 (3.0–95)	26.4 (5.8–106)	.4
Age group, No. (%)				
<24 mo	47 (62)	17 (61)	34 (49)	.1
24–59 mo	4 (5)	3 (11)	11 (16)	.05
≥60 mo	25 (33)	8 (29)	24 (35)	.8
Underlying condition, No. (%)[c]	26 (34)	9 (32)	25 (36)	.8
CNS disorder[d]	15 (20)	7 (25)	15 (22)	.7
Malignancy[e]	1 (1)	0 (0)	1 (1)	.99
Asplenia	1 (1)	0 (0)	2 (3)	.9
Hematologic disease[f]	0 (0)	0 (0)	3 (4)	.2
Others[g]	11 (14)	3 (11)	8 (12)	.6
Immunization status, No. (%)				
Adequately immunized	34 (45)	16 (57)	30 (44)	.9
Partially immunized	22 (29)	8 (29)	24 (35)	.5
Too young to be immunized	6 (8)	3 (11)	3 (4)	.6
Unimmunized	11 (15)	1 (4)	7 (10)	.4
Unknown	3 (4)	0 (0)	5 (7)	.6

Abbreviations: CNS, central nervous system; IQR, interquartile range.

[a] Episodes from 2010 are presented for reference only. Statistical analysis reflects comparison between 2007–2009 and 2011–2013 cases.

[b] One patient had 2 pneumococcal meningitis episodes in 2010 and 1 episode in 2011.

[c] Two, 1, and 4 patients had >1 underlying medical condition in 2007–2009, 2010, and 2011–2013, respectively.

[d] CNS disorders included head trauma with facial or skull fractures (n = 8), hydrocephalus with ventriculoperitoneal shunt (VPS) (n = 5), Klippel–Feil syndrome with dysmorphic temporal bone (n = 3 episodes, same patient), hypoxic-ischemic encephalopathy (n = 3), transsphenoidal repair of craniopharyngioma (n = 2), head trauma with arteriovenous fistula and hydrocephalus (n = 1), clival chordoma with cerebrospinal fluid (CSF) leak (n = 1), recent pineal tumor resection (n = 1), arachnoid cyst with VPS (n = 1), cribriform plate injury and CSF leak (n = 1), recent nasal repair of unspecified CSF leak (n = 1), Mondini malformation (n = 1), Chiari malformation with recurrent meningitis (n = 1), Dandy–Walker syndrome with hydrocephalus and VPS (n = 1), cochlear implant (n = 1), optic glioma (n = 1), Dandy–Walker syndrome (n = 1), Menkes syndrome (n = 1), and tuberous sclerosis (n = 1).

[e] Malignancy included acute lymphoblastic leukemia (n = 2).

[f] Hematologic disease included sickle cell disease (n = 2) and spherocytosis (n = 1).

[g] Others included history of prematurity (n = 6), trisomy 21 (n = 3), nephrotic syndrome (n = 1), polycystic kidney disease (n = 1), tetralogy of Fallot (n = 1), dextrocardia (n = 1), branchial cleft cyst (n = 1), maternal chorioamnionitis (n = 1), short gut (n = 1), complement deficiency (n = 1), severe congenital scoliosis (n = 1), hypothyroidism (n = 1), McCune Albright syndrome (n = 1), mucopolysaccharidosis (n = 1), and Turner syndrome (n = 1).

RESULTS

Characteristics of the Study Population

A total of 1207 IPD episodes occurred during the study period; 173 PM episodes (14%) were identified among 171 children. The proportion of PM among IPD episodes increased 50% (76/645 [12%] vs 69/394 [18%]; $P = .03$) from 2007–2009 to 2011–2013 (Figure 1). An 8-year-old girl with Klippel–Feil syndrome and dysmorphic temporal bone had 3 episodes of PM (February 2010, September 2010, and May 2011). Her first 2 episodes were caused by serotype 19A (pan-susceptible and pan-resistant, respectively), and the third episode by serotype 7F. The study population characteristics are shown in Table 1. Twelve patients (7%) were <2 months of age. Underlying conditions were more frequent in patients ≥24 months (36/75 [48%] vs 24/98 [24%]; $P = .001$). During the overall study period, a central nervous system (CNS) disorder was the most common underlying disorder (37/173 [21%]). A congenital or acquired/traumatic structural defect that allowed communication between the CNS and the nasopharynx, paranasal sinuses, mastoid air cells, or middle/inner ear was identified in 29 of 37 patients (78%).

Table 2. Serotype Distribution of Pneumococcal Isolates From Pediatric Patients With Pneumococcal Meningitis

Serotype	2007–2009 (n = 74)	2010[a] (n = 25)	2011–2013 (n = 67)	Total (%)
PCV13				
19A	20	6	10	36 (22)
7F	11	4	2	17 (10)
3	6	0	3	9 (5)
19F	0	0	2	2 (1)
9V	0	1	0	1 (1)
6B	0	0	1	1 (1)
4	1	0	0	1 (1)
18C	1	0	0	1 (1)
14	1	0	0	1 (1)
Non-PCV13				
22F	5	4	5	14 (8)
35B	4	2	6	12 (7)
15C	2	2	4	8 (5)
15B	5	1	1	7 (4)
10	3	0	4	7 (4)
6C	3	0	3	6 (4)
33F	0	1	5	6 (4)
23B	1	1	3	5 (3)
23A	1	0	4	5 (3)
15A	1	0	3	4 (2)
12F	2	1	1	4 (2)
9N	2	0	1	3 (2)
7C	1	0	2	3 (2)
21	0	1	2	3 (2)
8	1	1	0	2 (1)
16	1	0	1	2 (1)
11	0	0	2	2 (1)
37	0	0	1	1 (1)
35F	1	0	0	1 (1)
34	1	0	0	1 (1)
17	0	0	1	1 (1)

Abbreviation: PCV13, 13-valent pneumococcal conjugate vaccine.

[a] One patient had 2 episodes of pneumococcal meningitis in 2010. Both episodes were caused by serotype 19A; however, the isolates had different antibiotic susceptibility. The first isolate was pan-susceptible and the second was pan-resistant.

Table 3. Neuroimaging Study Results From Pediatric Patients With Pneumococcal Meningitis

Neuroimaging Finding[a]	2007–2009 (n = 67), No. (%)	2010[b] (n = 26), No. (%)	2011–2013 (n = 58), No. (%)	*P* Value
Normal study	17 (25)	7 (27)	15 (26)	.9
Sinus or mastoid cell opacification	26 (39)	5 (19)	17 (29)	.3
Infarct	11 (16)	7 (27)	15 (26)	.3
Subdural effusion	13 (19)	6 (23)	11 (19)	.99
Hydrocephalus/ ventriculomegaly	13 (19)	4 (15)	12 (21)	.99
Cerebral edema	9 (13)	3 (12)	6 (10)	.8
Subdural empyema[c]	1 (1)	0 (0)	9 (16)	.006
Cerebral vein and/or sinus thrombosis	3 (4)	2 (8)	4 (7)	.7
Intracranial hemorrhage[d]	2 (3)	2 (8)	3 (5)	.7
Intraparenchymal abscess	1 (1)	1 (4)	2 (3)	.6
Other[e]	11 (16)	3 (12)	7 (12)	.5

[a] Includes computed tomographic scan and/or magnetic resonance imaging findings.

[b] Episodes from 2010 are presented for reference only. Statistical analysis reflects comparison between 2007–2009 and 2011–2013 cases.

[c] The following serotypes were isolated from cases of subdural empyema: serotype 3 in 2007–2009; and serotype 35B (n = 2), serotypes 3, 10, 15C, 22F, 23A, and 33F (n = 1 each), and 1 nonviable isolate in 2011–2013.

[d] Includes subdural, subarachnoid, and intraparenchymal hemorrhage.

[e] Others included leptomeningeal enhancement (n = 5), facial and cranial fractures involving the sinuses and/or internal auditory canal (n = 5), white matter atrophic changes (n = 4), pus in ventricles (n = 1), cerebellar herniation (n = 1), pneumocephalus (n = 1), left cribriform plate defect with nasal encephalocele (n = 1), diffuse spasm of arteries (n = 1), increase in subarachnoid space (n = 1), and cystic encephalomalacia (n = 1).

Clinical Presentation and Laboratory Results

At admission, 159 of 173 (92%) episodes involved presentation with fever, and 38 of 173 (22%) had new-onset prehospitalization seizures; these rates remained stable between 2007–2009 and 2011–2013. The overall median length of fever prior to admission was 2.0 days (interquartile range [IQR], 1.0–3.0 days). No statistical differences were observed in CSF or blood laboratory results between 2007–2009 and 2011–2013 (Supplementary Table 1).

Serotype Distribution

One hundred sixty-six pneumococcal isolates (96%) were viable for serotyping (Table 2). Serotype 19A was the most common serotype isolated (22%), followed by serotype 7F (10%). The proportion of PCV13 serotype cases decreased from 54% in 2007–2009 to 27% in 2011–2013 (−50%; $P = .001$). The 3 most common serotypes were 19A (27%), 7F (15%), and 3 (8%) in 2007–2009; and 19A (15%), 35B (9%), and 22F (8%) in 2011–2013. After the introduction of PCV13, serotype 19A decreased from 27% to 15% of isolates (−44%; $P = .08$), serotype 7F from 15% to 3% (−80%; $P = .02$), and serotype 3 from 8% to 5% (−38%; $P = .5$). Ten children with PM due to serotype 19A were identified in 2011–2013; 3 were adequately immunized and 7 were partially immunized. The most common non-PCV13 serotypes during 2011–2013 were 35B (12%), 22F (10%), and 33F (10%). The only difference between the demographic characteristics, clinical presentation, and laboratory results for PM due to PCV13 vs non-PCV13 serotypes was the distribution of patient race/ethnicity (Supplementary Table 2).

Table 4. Clinical Course and Outcomes of Pediatric Patients With Pneumococcal Meningitis

Clinical Course and Outcome	2007–2009 (n = 76), No. (%)	2010[a] (n = 28), No. (%)	2011–2013 (n = 69), No. (%)	*P* Value
Intensive care unit admission	50 (66)	21 (75)	52 (75)	.4
Mechanical ventilation	26 (34)	12 (43)	29 (42)	.6
Neurosurgery[b]	10 (13)	3 (11)	4 (6)	.2
Clinical complications	30 (39)	11 (39)	24 (35)	.8
New seizures after admission	10 (13)	4 (14)	12 (17)	.5
Cranial nerve palsy	11 (14)	2 (7)	4 (6)	.1
Hemiparesis[c]	1 (1)	1 (4)	8 (12)	.01
Other motor deficit	3 (4)	2 (7)	4 (6)	.7
Herniation	4 (5)	2 (7)	3 (4)	.99
Other	8 (11)	3 (11)	8 (12)	.99
Fever after admission, d, median (IQR)	2 (1.0–4.0)	3 (1.0–5.0)	3 (1.0–5.0)	.4
Length of hospital stay, d, median (IQR)	10 (7.0–16.0)	13 (10.0–18.8)	11 (7.8–15.5)	.99
Length of antibiotic therapy, d, median (IQR)	13.5 (10.0–15.0)	13 (10.0–14.0)	13 (10.0–17.0)	.9
Case-fatality rate	3 (4)	2 (7)	7 (10)	.3

Abbreviation: IQR, interquartile range.

[a] Episodes from 2010 are presented for reference only. Statistical analysis reflects comparison between 2007–2009 and 2011–2013 cases.

[b] Neurosurgery procedures included placement of external ventricular drain (n = 9), removal of ventriculoperitoneal shunt (VPS) prior to identification of organism and replacement of VPS (n = 4), removal of VPS plus drainage of empyema (n = 2), and drainage of empyema alone (n = 2).

[c] The following serotypes were isolated from cases of hemiparesis: serotype 3 in 2007–2009; serotype 19A in 2010; and serotypes 10 (n = 2), 22F (n = 2), 12F, 19A, 19F, and 3 (n = 1 each) in 2011–2013.

Antibiotic Susceptibility

In 2007–2009, 75% of the isolates had a penicillin MIC ≤0.06 μg/mL and 25% a penicillin MIC ≥0.12 μg/mL; these rates remained unchanged after the introduction of PCV13. PCV13 serotypes were more commonly associated with a penicillin MIC ≥0.12 μg/mL than non-PCV13 serotypes (39% vs 16%; $P = .001$). The most common serotypes with a penicillin MIC ≥0.12 μg/mL were 19A (n = 24) and 35B (n = 9). Overall, 92% of isolates had a ceftriaxone MIC ≤0.5 μg/mL and 8% a ceftriaxone MIC ≥1 μg/mL. After the introduction of PCV13, the percentage of isolates with a ceftriaxone MIC ≥1 μg/mL decreased from 13% to 3% (−77%; $P = .03$). No isolates with a ceftriaxone MIC ≥2 μg/mL were identified in 2011–2013. All the pneumococcal isolates with a ceftriaxone MIC ≥1 μg/mL and penicillin MIC ≥2 μg/mL were serotype 19A.

Neuroimaging Findings, Clinical Course, and Complications

Neuroimaging studies were performed in 151 episodes (87%); 112 (74%) had abnormal findings. After the introduction of PCV13, subdural empyema increased from 1% to 16% ($P = .006$) in imaged patients; other neuroimaging findings remained unchanged (Table 3).

There were no differences in the rates of patients requiring intensive care, mechanical ventilation, neurosurgery, or development of complications after the introduction of PCV13 (Table 4). The most common clinical complications were new-onset seizures after admission (26/173 [15%]) and cranial nerve palsy (17/173 [10%]). Hemiparesis increased from 1% in 2007–2009 to 12% in 2011–2013 ($P = .01$); this finding was not associated with the increase of subdural empyema cases or any particular serotype. Cranial nerve palsy was the only complication significantly associated with PCV13 serotypes (12/69 [17%] vs 4/97 [4%]; $P = .006$). Clinical complications did not correlate with penicillin or ceftriaxone MICs (data not shown).

Antibiotic Use

In 106 of 173 episodes (61%), antibiotic therapy was provided for 10–14 days. Among the survivors, 4 episodes were treated for 8–9 days and 51 episodes for >14 days. In 164 episodes (95%), ceftriaxone or cefotaxime plus vancomycin was used as initial empiric therapy. In 2011–2013, 8 of 67 patients (11%) completed antibiotic therapy with ceftriaxone or cefotaxime plus vancomycin; however, only 2 of them required both antibiotics based on bacterial meningitis treatment guideline recommendations [23]. Overall, 123 of 166 isolates (74%) were susceptible to penicillin and ceftriaxone; 23 of 123 patients (19%) transitioned to penicillin to complete therapy after susceptibilities were available.

Case-Fatality Rate, Sequelae, and Follow-up

There were 12 fatal cases (7%). CFRs were 4% in 2007–2009 and 10% in 2011–2013 ($P = .3$). The fatal cases were related to serotypes 19A (n = 3), 15C (n = 2), 15A, 15B, 19F, 7F, 9V, 3, and 35B (n = 1 each). Of the overall fatal cases, 75% occurred in children aged <24 months, 67% were adequately immunized, and 50% had an underlying condition. Fatal cases did not correlate with high antibiotic MICs.

Table 5. Univariate and Multivariate Logistic Regression Analyses of Predictor Factors for Sequelae

Variable	Univariate Analysis OR (95% CI)	*P* Value	Multivariate Analysis OR (95% CI)	*P* Value
Seizures prior to admission	7.59 (2.76–20.89)	<.0001	4.31 (1.31–14.22)	.02
Intensive care unit admission	3.83 (1.87–7.85)	<.0001	3.04 (1.12–8.25)	.03
Mechanical ventilation	6.25 (2.95–13.24)	<.0001	3.40 (1.30–8.90)	.01
Abnormal neuroimaging findings	4.50 (2.00–10.12)	<.0001	3.99 (1.57–10.15)	.004
Neurosurgery	3.34 (1.04–10.74)	.04	1.73 (.39–7.59)	.5

Abbreviations: CI, confidence interval; OR, odds ratio.

Of the 161 survivors, 84 (52%) had at least 1 sequela at the time of discharge. The most common sequela was sensorineural hearing loss (SNHL), at 31%. Forty-one patients (25%) were discharged receiving antiepileptic drugs. At discharge, motor impairment was present in 24 of 161 patients (15%), cranial nerve palsy in 11 of 161 (6%), and cortical blindness in 1 of 161 (1%); these rates remained stable after the introduction of PCV13 (Supplementary Table 3). Rates of sequelae were similar between PCV13 and non-PCV13 serotype cases (36/62 [58%] vs 45/92 [49%]; $P = .3$). Predictor factors for sequelae are shown in Table 5. The median follow-up time was 1.06 years (IQR, 0.13–3.21 years). A follow-up visit was available in 138 of 161 patients (86%); 54 (39%) had persistence of sequelae. Of 138 patients, 31 (22%) had SNHL, 15 (11%) had motor impairment, 14 (10%) still required antiepileptic drugs, 7 (5%) required a cochlear implant, and 7 (5%) had developmental/language delay.

Patients With and Those Without Underlying Conditions

The median length of fever prior to admission was 1 day longer in previously healthy patients compared to patients with underlying conditions ($P = .001$). Previously healthy patients were more likely than those with underlying conditions to have new-onset seizures prior to presentation, abnormal neuroimaging findings, and sequelae (Table 6).

Table 6. Comparison of Pediatric Patients Diagnosed With Pneumococcal Meningitis With or Without an Underlying Condition From 2007 to 2013

Characteristic	No Underlying Condition (n = 113), No. (%)	Underlying[a] Condition (n = 60), No. (%)	*P* Value
Fever prior to admission, d, median (IQR)	2 (1.0–3.0)	1 (1.0–2.7)	.001
Seizures prior to admission	30 (27)	8 (13)	.05
PCV13 serotype[b]	47/110 (43)	22/56 (39)	.7
Intensive care unit admission	80 (71)	43 (72)	.99
Mechanical ventilation	39 (35)	28 (47)	.1
Clinical complications	46 (41)	19 (32)	.3
Neuroimaging	96 (85)	55 (92)	.2
Abnormal neuroimaging results	79/96 (82)	33/55 (60)	.004
Neurosurgery	9 (8)	8 (13)	.3
Fever after admission, d, median (IQR)	3 (1.0–5.0)	2 (1.0–4.0)	.2
Length of hospital stay, d, median (IQR)	11 (8.0–15.0)	14 (7.0–20.0)	.4
Length of antibiotic therapy, d, median (IQR)	13 (10.0–15.0)	13 (10.0–17.0)	.5
Case-fatality rate	6 (5)	6 (10)	.3
Sequelae present[c]	65/107 (61)	19/54 (35)	.003
SNHL	32/107 (30)	15/54 (28)	.9
Motor impairment	18/107 (17)	6/54 (11)	.3
Cranial nerve palsy	11/107 (10)	0/54 (0)	.02
Discharged on AED	34/107 (32)	7/54 (13)	.01

Abbreviations: AED, antiepileptic drug; IQR, interquartile range; PCV13, 13-valent pneumococcal conjugate vaccine; SNHL, sensorineural hearing loss.

[a] Three episodes correspond to 1 patient. This patient only had sequelae after the last episode.

[b] Pneumococcal isolates were not viable in 3 cases in 2007–2009 and in 4 cases in 2011–2013.

[c] Denominators for sequelae exclude fatal cases.

Dexamethasone Use

Dexamethasone was used in a total of 60 episodes (35%), but was adequate in only 22 episodes (13%). We compared the 22 children who received adequate dexamethasone to 113 children who did not receive any dexamethasone. Indirect markers of disease severity (intensive care, mechanical ventilation, and neurosurgery) and rates of clinical complications, sequelae, and case fatality were comparable between the groups ($P > .5$ for each) (Supplementary Table 4).

DISCUSSION

Our study revealed that after the introduction of PCV13, the number of cases of PM per year remained unchanged among 8 children's hospitals. The proportion of PM cases due to PCV13 serotypes decreased to 27% of cases; however, serotype 19A continued to be the most common serotype. Ceftriaxone nonsusceptible isolates significantly decreased, representing only 3% of all isolates in 2011–2013.

A decline of 56%–67% of PM among US children <5 years of age was reported within the first 2–5 years after PCV7 introduction [5, 14, 15, 24]. Few studies reported the impact of PCV7 on PM during the late post-PCV7 period. The ABCs network showed a slight uptrend of the incidence of PM among children aged 2–23 months from 2002–2003 to 2006–2007 (3.32 to 3.67 cases per 100 000 population) [1]. Moreover, the incidence of PM among patients aged 11–17 years remained unchanged from 1998 to 2007 [1]. A study from France reported that the number of PM cases did not decrease significantly from 2001–2002 to 2007–2008 due to an increase of cases among children ≥2 years old [25]. We previously reported a stable number of PM cases between 2007 and 2010 [17]. Likewise, we did not observe a decline in the number of PM cases in this current study. We observed only a modest decrease in PM among children <24 months old. Overall, our study population median age was higher than previously reported for PM [3, 6, 11]. Two reports from Europe describe the impact of PCV13 on PM in children [11, 26]. Moore et al reported no change in the burden of PM as a proportion of documented IPD cases among children <2 years old from 1996 to 2013 in the Oxfordshire region of England [26]. Levy et al reported a 27.4% reduction in PM among all the bacterial meningitis cases from 2009 to 2012 in France [11]. Factors contributing to the different findings between Levy et al study and our study include their larger sample size, their lower proportion of children with underlying conditions, higher median age in our study population, and differences in serotype distribution.

We observed a significant change in the serotype distribution after PCV13 introduction. Although serotype 19A decreased 44% from 2007–2009 to 2011–2013, it remained the most common serotype in 2011–2013. In France, serotype 19A also remained a significant cause of PM by 2012 [11]. In our study, non-PCV13 serotypes accounted for 73% of all isolates in 2011–2013; serotype 35B and 22F were the most common non-PCV13 serotypes. In another US study, serotype 35B was the most common non-PCV13 serotype among invasive and noninvasive isolates, particularly among children aged 0–5 years [27]. Serotype 22F was reported as the second most common non-PCV7 serotype causing meningitis in the United States in 2004–2005 among all age groups [5]. In contrast, serotype 12F was the most common non-PCV13 serotype causing PM in France in 2011–2012 [11].

After the introduction of PCV13, we found a significant decline in ceftriaxone-nonsusceptible isolates (MIC ≥1 μg/mL) from 13% to 3%. No ceftriaxone-resistant isolates (MIC ≥2 μg/mL) were identified in 2011–2013, similar to the recent study from France [11]. These changes were closely related to the decline of serotype 19A. An increasing predominance of penicillin-nonsusceptible non-PCV13 serotypes, such as 35B in the United States [27], warrants continuous monitoring of pneumococcal isolates.

In our study, severe outcomes were not associated with any particular serotype with the exception of cranial nerve palsy, which was more associated with PCV13 than non-PCV13 serotypes. Previous reports have not identified a correlation between vaccine serotypes and PM outcomes, including CFR [1, 6, 28]. CFR and sequelae were not associated with penicillin or ceftriaxone MICs in our study as previously reported; however, the use of vancomycin along with ceftriaxone or cefotaxime as empiric therapy and our sample size may limit this analysis [3, 12, 29–31]. The identified factors that significantly correlated with neurologic sequelae may help clinicians assess prognosis of children early in the course of PM management.

We observed an increase in hemiparesis and subdural empyema in the post-PCV13 period; the reasons for these findings are not apparent and may represent random variation.

Pneumococcal meningitis has been associated with higher rates of SNHL than any other bacterial meningitis [32, 33]. In this study, SNHL represented the most common sequela, consistent with other reports [3, 28]. In contrast, Stockmann et al reported developmental delay (43%) as the most common sequela in children with PM, followed by seizures (31%) and SNHL (29%) [6]. Behavioral/intellectual disorders have been described as the most common long-term sequela in bacterial meningitis [34]. Our study follow-up median length was significantly shorter than reported by Stockmann et al [6], which could explain the different results.

As expected, children ≥2 years old with PM had a higher rate of underlying conditions, most of which were related to a meningeal breach, as previously noted [3, 11]. More abnormal neuroimaging findings and sequelae occurred among previously healthy children than among children with underlying conditions, which may be related to the longer period of fever prior

to admission (and possibly meningeal inflammation) observed among previously healthy children.

Our study was not designed to assess the effects of dexamethasone as adjuvant therapy for PM; however, we also did not find any outcome differences between patients who did or did not receive dexamethasone [3, 35–37]. The value of dexamethasone for PM in pediatrics remains inconclusive [38].

There are limitations to our study. First, our group only identifies culture-confirmed cases, likely underestimating the true number of cases of PM and IPD. Second, incomplete medical records and the lack of homogeneity for neurology evaluations may have an impact on our data interpretation. Third, the specific neuroimaging study performed in each patient was not captured; differences in imaging techniques may have influenced our neuroimaging results. Fourth, 4% of isolates were nonviable for serotyping and MIC determination. Last, non–statistically significant results in subgroup analyses may be due to a small sample size.

In conclusion, after the introduction of PCV13, we did not observe a decrease in the number of cases of PM among 8 children's hospitals, although the proportion of cases caused by PCV13 serotypes significantly decreased. Overall, morbidity and CFR have not been significantly impacted by routine use of PCV13. Also, ceftriaxone-nonsusceptible isolates significantly decreased in 2011–2013, with no isolates with a ceftriaxone MIC ≥2 μg/mL. If this trend continues, vancomycin may no longer be required as empiric therapy in addition to ceftriaxone or cefotaxime for children who are fully immunized with PCV13. Nonsusceptibility to penicillin is still relatively high; therefore, ceftriaxone or cefotaxime should continue to be the antibiotic of choice for empiric therapy. Ongoing surveillance is warranted to continue to assess the impact of PCV13 on PM in children.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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