Invasive Pneumococcal Disease in Children's Hospitals: 2014–2017

Sheldon L. Kaplan, MD,[a] William J. Barson, MD,[b] Philana Ling Lin, MD,[c] José R. Romero, MD,[d] John S. Bradley, MD,[e] Tina Q. Tan, MD,[f] Pia S. Pannaraj, MD,[g] Laurence B. Givner, MD,[h] Kristina G. Hulten, PhD[a]

abstract

BACKGROUND: The 13-valent pneumococcal conjugate vaccine (PCV13) was licensed in the United States in 2010. We describe invasive pneumococcal disease (IPD) in children at 8 children's hospitals in the US from 2014 to 2017.

METHODS: Children with IPD occurring from 2014 to 2017 were identified from a prospective study. Demographic and clinical data, including results of any immune evaluation along with the number and dates of previous pneumococcal conjugate vaccines administered, were recorded on case report forms. Isolate serotypes were determined in a central laboratory. Pneumococcal conjugate vaccine doses were counted if IPD occurred ≥2 weeks after a dose.

RESULTS: PCV13 serotypes accounted for 23.9% (115 out of 482) of IPD isolates from 2014 to 2017. Serotypes 3, 19A, and 19F accounted for 91% of PCV13 serotypes. The most common non-PCV13 serotypes were 35B, 23B, 33F, and 22F. An underlying condition was significantly ($P < .0001$) more common in children with IPD due to non-PCV13 serotypes (200 out of 367, 54.5%) than for children with PCV13 serotypes (27 out of 115, 23.5%). An immune evaluation was undertaken in 28 children who received ≥2 PCV13 doses before IPD caused by a PCV13 serotype. Only 1 was found to have an immunodeficiency.

CONCLUSIONS: PCV13 serotypes (especially serotypes 3, 19A, and 19F) continue to account for nearly a quarter of IPD in US children 4 to 7 years after PCV13 was introduced. Underlying conditions are more common in children with non-PCV13 serotype IPD. Immune evaluations in otherwise healthy children with PCV13 serotype IPD despite receiving ≥2 PCV13 doses did not identify an immunodeficiency.

[a]*Department of Pediatrics, Pediatric Infectious Diseases Section, Texas Children's Hospital and Baylor College of Medicine, Houston, Texas;* [b]*Department of Pediatrics, Nationwide Children's Hospital and College of Medicine and Public Health, The Ohio State University, Columbus, Ohio;* [c]*Department of Pediatrics, Children's Hospital of Pittsburgh of the University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania;* [d]*Department of Pediatrics, Arkansas Children's Hospital and University of Arkansas for Medical Sciences, Little Rock, Arkansas;* [e]*Department of Pediatrics, Rady Children's Hospital–San Diego and University of California, San Diego, San Diego, California;* [f]*Department of Pediatrics, Ann and Robert H. Lurie Children's Hospital of Chicago and Feinberg School of Medicine, Northwestern University, Chicago, Illinois;* [g]*Department of Pediatrics, Children's Hospital Los Angeles and School of Medicine, University of Southern California, Los Angeles, California; and* [h]*Department of Pediatrics, Brenner Children's Hospital and Wake Forest School of Medicine, Wake Forest University, Winston-Salem, North Carolina*

Dr Kaplan conceptualized and designed the study and drafted the initial manuscript; Dr Hulten manages the study database and conducted the initial analyses; Drs Barson, Ling, Romero, Bradley, Tan, Pannaraj, and Givner coordinated and supervised data collection at their sites; and all authors reviewed and revised the manuscript and approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

DOI: https://doi.org/10.1542/peds.2019-0567

Accepted for publication Jun 17, 2019

WHAT'S KNOWN ON THIS SUBJECT: Invasive pneumococcal disease (IPD) has decreased in US children since the introduction of the 7-valent pneumococcal conjugate vaccine in 2000 followed by the 13-valent pneumococcal conjugate vaccine (PCV13). The majority of IPD cases in children are now due to non-PCV13 serotype isolates.

WHAT THIS STUDY ADDS: A majority of children with IPD due to non-PCV13 serotype isolates have an underlying condition. Immune evaluation for an otherwise healthy child with IPD caused by a PCV13 serotype isolate despite having received ≥2 PCV13 doses is unlikely to be revealing.

To cite: Kaplan SL, Barson WJ, Lin PL, et al. Invasive Pneumococcal Disease in Children's Hospitals: 2014–2017. *Pediatrics.* 2019;144(3):e20190567

Invasive pneumococcal disease (IPD) in children decreased substantially in the United States after the routine administration of the 7-valent pneumococcal conjugate vaccine (PCV7) (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) beginning in 2000, followed by the 13-valent pneumococcal conjugate vaccine (PCV13) (additional serotypes 1, 3, 5, 6A, 7F, 19A) in 2010.[1–4] The 23-valent pneumococcal polysaccharide vaccine (PPSV23) (contains, in addition to PCV13 serotypes [except 6A], 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F) is also recommended in addition to PCV13 for children 24 months to 18 years of age with select underlying conditions. PCV13 serotype isolates still account for a considerable proportion of IPD cases occurring among US children, but detailed descriptions of cases are sparse, especially regarding receipt of previous pneumococcal conjugate vaccines (PCVs) and the presence or absence of an underlying condition.

In case series and reports from around the world, researchers have described several children who have developed IPD due to PCV13 serotype isolates despite having received at least 2 doses of PCV13 or 1 dose of PCV7 or PCV13 as a toddler.[5–12] Serotypes 3, 19A, and 19F were the most common serotypes from the patients, none of which included patients from the United States. Almost all of the patients either did not undergo immune evaluation or had normal results of immune workups.

In a study of IPD among patients <18 years old in Massachusetts from 2002 through 2014, 22.1% of patients had at least 1 comorbidity.[13] An immunosuppressive condition was most common, followed by prematurity or low birth weight and neurologic disease. Comorbidities were less prevalent among IPD cases caused by the 6 additional serotypes in PCV13 (19%) than for IPD cases due to the original 7 serotypes in PCV7 (32%) or IPD cases due to non-PCV13 serotypes (26%). Public Health England reported that from 2006 through 2014, 22% of children with IPD due to a PCV7 or PCV13 serotype isolate had an underlying comorbidity, mainly malignancy or immunosuppression followed by cardiac abnormalities.[14]

In this study, we describe the epidemiology of IPD in children at 8 children's hospitals in the United States over the years 2014–2017, with analysis of the site of infection, prevalence of underlying conditions, antimicrobial susceptibility, and receipt of pneumococcal vaccines stratified by cases caused by PCV13 versus non-PCV13 serotype isolates. A secondary aim was to describe the immunologic evaluations of children with IPD caused by PCV13 serotype isolates who received at least 2 doses of PCVs before infection.

METHODS

The US Pediatric Multicenter Pneumococcal Surveillance Study Group consists of investigators from 8 children's hospitals (Houston, TX; Pittsburgh, PA; Little Rock, AR; San Diego, CA; Los Angeles, CA; Chicago, IL; Columbus, OH; and Winston-Salem, NC) who have been prospectively identifying children with IPD since September 1993.[15] We identified infants and children with IPD from our database seen between January 1, 2014, and December 31, 2017. IPD was documented by positive culture results from a normally sterile site (blood, cerebrospinal fluid, pleural fluid, synovial fluid, peritoneal fluid, etc). The diagnosis of pneumococcal pneumonia required an abnormal chest radiograph result plus a positive culture result from blood, pleural fluid, or lung. Mastoiditis was also considered an invasive infection for which isolates were obtained from middle ear fluid, subperiosteal abscess, or mastoid bone. The approach to obtaining blood cultures in children with fever without a source was inconsistent among the 8 children's hospitals. Demographic and clinical information was collected retrospectively and recorded on a standard case report form for each episode of infection.

Administration of PCV7 or PCV13 was documented through the patient's medical records by contacting the patient's health care provider or in a vaccine registry. Invasive disease due to a vaccine serotype isolate occurring after receipt of PCV7 or PCV13 was counted only if the infection occurred at least 2 weeks after receipt of a PCV. A supplemental case report form for any immune evaluation testing was completed for patients who had received ≥2 PCV doses before their IPD episode if due to a PCV13 serotype isolate. The study has been reviewed by the institutional review boards of each of the participating hospitals.

The patient database was maintained in a central office (Texas Children's Hospital and Baylor College of Medicine, Houston, TX). Pneumococcal isolates were identified by using standard methods in the microbiology laboratories of each hospital and sent to a central laboratory for further testing (Dr Edward O. Mason, Jr, Infectious Disease Research Laboratory, Texas Children's Hospital, Houston, TX). Isolates were serotyped by the capsular swelling method by using commercially available antisera (Statens Serum Institut, Copenhagen, Denmark; Cedarlane Laboratories, Inc, Burlington, NC).[15]

Minimal inhibitory concentrations (MICs) for penicillin and ceftriaxone were performed and interpreted by standard methods.[16] For noncentral nervous system infections, isolates were considered susceptible to parenteral penicillin if MICs were ≤2.0 μg/mL or to ceftriaxone if MICs were ≤1.0 μg/mL. For central

TABLE 1 Number of PCV13 and Most Common Non-PCV13 Serotype Isolates Causing IPD at 8 US Children's Hospitals, 2014–2017

PCV13 Serotypes, *N* = 115		Non-PCV13 Serotypes, *N* = 367	
Serotype	No.	Serotype	No.
3	48	35B	44
19A	33	23B	37
19F	24	33F[a]	36
7F	5	22F[a]	32
23F	2	10A[a]	19
14	2	15C[a]	19
18C	1	23A	18
		15A	15
		15B[a]	15
		6C	15
		16F	14
		12F[a]	11
		Other	92

PCV13 includes serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. PCV7 contained serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F.

[a] Serotypes that are included in PPSV23 but not PCV13.

nervous system infections, isolates were considered susceptible to parenteral penicillin if MICs were ≤0.06 μg/mL or to ceftriaxone if MICs were ≤0.5 μg/mL. Susceptibility data were not available for all isolates.

Statistical analysis was performed by using Fisher exact or Wilcoxon rank sum tests (Stata11; College Station, TX).

RESULTS

A total of 495 patients were identified over the years 2014–2017; 13 patients had no isolate and were excluded from the study (in Supplemental Fig 3, we show the annual number of IPD cases). Age distribution did not differ between patients with IPD due to PCV13 serotype versus non-PCV13 serotype isolates (Supplemental Fig 4). The total number of PCV13 and most common non-PCV13 serotype isolates are shown in Table 1. Overall, PCV13 serotype isolates accounted for 23.9% (115 out of 482) and non-PCV13 serotype isolates for 76.1% (367 out of 482) of IPD isolates over the 4 years of this study. PCV13 serotype isolates accounted for 20% (26 out of 128), 27% (29 out of 108), 25% (31 out of 124), and 24% (29 out of 122) of IPD cases in 2014, 2015, 2016, and 2017, respectively. The most common PCV13 serotypes were 3, 19A, and 19F, which together accounted for 91% of these isolates.

The most common non-PCV13 serotypes were 35B, 23B, 33F, and 22F, all of which combined accounted for 41% (149 out of 367) of these isolates. Serogroup 15 (serotypes 15A, 15B, and 15C) in aggregate accounted for 13% (49 out of 367) of the isolates. The sites of IPD caused by PCV13 serotype versus non-PCV13 serotype isolates are shown in Table 2. The distribution of sites of infection differed significantly ($P < .0001$) between the 2 groups. Pneumonia was the most common site of infection for PCV13 serotype isolates, whereas bacteremia was the most common site for non-PCV13 serotype isolates.

TABLE 2 Sites of IPD for PCV13 Versus Non-PCV13 Serotype Isolates at 8 US Children's Hospitals, 2014–2017

Site of Infection	PCV13 Serotypes[a], *N* = 115, *n* (%)	Non-PCV13 Serotypes, *N* = 367, *n* (%)
Bacteremia	25 (21.7)	182 (49.6)
Pneumonia	50 (43.5)	69 (18.8)
Meningitis	12 (10.4)	70 (19.1)
Mastoiditis	22 (19.1)	12 (3.3)
Bone and joint	2 (1.7)	18 (4.9)
Peritonitis	0 (0)	4 (1.1)
Other[b]	4 (3.5)	12 (3.3)

[a] Distribution of sites differs significantly ($P < .0001$) for infections due to PCV13 versus non-PCV13 isolates.

[b] Other sites included orbital cellulitis-4, endophthalmitis-3, intracranial abscess-3, epidural abscess-2, subdural abscess-1, subperiosteal abscess-1, sinusitis with intracranial extension-1, and endocarditis-1.

Underlying Conditions

An underlying condition was significantly ($P < .0001$) more common among patients with IPD due to non-PCV13 serotype isolates (200 out of 367, 54.5%) compared with patients with IPD caused by PCV13 serotype isolates (27 out of 115, 23.5%) (Table 3). Leukemia and other malignancies were the most common underlying conditions for patients with non-PCV13 serotype isolates. Only non-PCV13 serotype isolates were recovered from the 17 children with hemoglobinopathies or asplenia. Children with underlying conditions were significantly older than patients without underlying conditions ($P < .001$) (Supplemental Fig 5).

PCV13 Serotype Infections

The distribution of PCV13 serotypes and the number of PCV13 or PCV7 doses before IPD are shown in Table 4. (Data on vaccine status were not available for 10 children.) For the 105 children for whom PCV status was known, 30 had not received a PCV and 14 had received 1 dose before their IPD. Of the 30 children who had not received a PCV, 22 (73%) were of an age at the time of IPD for which ≥2 doses of PCV were recommended. Two, 3, or 4 doses

TABLE 3 Underlying Conditions for Patients With IPD Caused by PCV13 Versus Non-PCV13 Serotype Isolates at 8 US Children's Hospitals, 2014–2017

Underlying Condition	PCV13 Serotypes, *n* (%)	Non-PCV13 Serotypes, *n* (%)
None	88 (76.5)	167 (45.5)
Malignancy	8 (7.0)	57 (15.5)
Central nervous system	1 (0.9)	17 (4.6)
Genetic	6 (5.2)	20 (5.5)
Cardiovascular	3 (2.6)	16 (4.4)
Transplant	1 (0.9)	16 (4.4)
Renal	3 (2.6)	11 (3.0)
Hemoglobinopathy	0	13 (3.5)
Immunodeficiency or autoimmune	3 (2.6)	9 (2.5)
Prematurity	0	8 (2.2)
Asplenia	0	4 (1.1)
Other[a]	2 (1.7)	29 (7.9)
Total underlying conditions	27 out of 115 (23.5)	200 out of 367 (55.3)*

[a] Supplemental Table 6 lists all "Other" underlying conditions.
* $P < .0001$.

were received by 6, 18, and 37 children, respectively. Twenty-four children had an underlying condition. Children with serotype 3 isolates causing their IPD were significantly less likely ($P < .0001$) to have an underlying condition (1 out of 45) than children with infections due to serotype 19A (10 out of 28) or serotype 19F (9 out of 24).

Twenty-two children with underlying conditions received PPSV23 before their IPD episode. Six had IPD due to a PPSV23 but non-PCV13 serotype organism (one each of serotypes 8, 10A, 15B, 15C [considered B/C], 22F, 33F). Five had IPD due to a 23A serotype organism, and 3 had IPD due to a 15B serotype organism. None had a PCV13 serotype isolate.

An immune evaluation of some type was documented in 28 of 61 children who received at least 2 doses of PCV13 and whose IPD was caused by a PCV13 serotype isolate (or PCV7 if a PCV7 serotype isolate caused their IPD) (Table 5). Of these 28 patients, one had a slightly low immunoglobulin M (40 mg/dL; normal for age: 44–155 mg/dL); a child with pre–B cell acute lymphocytic leukemia had a low immunoglobulin G (IgG) (377 mg/dL; normal for age: 423–1090 mg/dL) and low antibody count to the causative serotype (19F, 0.4 μg/mL with a level >15 μg/mL, considered protective by the laboratory performing the test). Another child with acute lymphocytic leukemia had low immunoglobulin A (22 mg/dL; normal for age: 54–150 mg/dL) and had a low antibody count to the causative serotype (19F, 0.26 μg/mL), and 1 had no protective antibody to tetanus toxin on a humoral immune panel. One patient who had received 4 doses of PCV13 was found to have a diagnosis of common variable immunodeficiency (CVID) established as a result of evaluating quantitative immunoglobulins (IgG: 332 mg/dL [normal for age: 546–1533 mg/dL]; immunoglobulin M: 53 mg/dL [normal for age: 21–95 mg/dL]; immunoglobulin A: 53 mg/dL [normal for age: 54–150 mg/dL]) after having pneumococcal meningitis due to a serotype 23F isolate at 3 years of age. However, this patient had a family history of CVID in a maternal grandfather, aunt, and cousin. One patient had abnormal T-cell testing, but no specific immunodeficiency disorder was assigned (testing was done on day 4 of IPD). Fifteen children had antibody measured to the serotypes (serotype 3, $n = 9$; 19F, $n = 5$; 19A, $n = 1$) causing their infection. All but 3 (2 patients with leukemia, another with a renal transplant) had concentrations much above those considered protective or normal by the laboratory performing the test.

TABLE 4 PCV13 Serotypes Causing IPD in Children at 8 US Children's Hospitals and the Number of PCV Doses Received, 2014–2017

	No. PCV13 Doses Before IPD[a], *n* (No. Children With Underlying Conditions)					
Serotype	0	1	2	3	4	Total Cases
3	11 (1)	8	3	10	13	45
19A	10 (5)	2 (1)	2	3	11 (4)	28
19F	4	4 (2)	1	4 (1)	11 (6)[b]	24
7F	4 (1)	0	0	0	0	4
14	1	0	0	0	1 (1)	2
18C	0	0	0	0	0	0
23F	0	0	0	1 (1)	1 (1)	2
Total	30	14	6	18	37	105

[a] PCV7 doses were included for serotypes 14, 18C, 19F, and 23F; vaccine status was unknown or not documented for 10 children (serotype 19A-5, serotype 3-3 [one with leukemia], serotype 7F-1, serotype 18C-1).
[b] One child with leukemia had 5 PCV13 doses.

Antibiotic Susceptibility

The distributions of MICs for penicillin and ceftriaxone for PCV13 serotype and non-PCV13 serotype isolates are shown in Figs 1 and 2. The proportion of isolates with penicillin MIC ≤2.0 μg/mL was significantly greater ($P < .0001$) for non-PCV13 serotype isolates (339 out of 340) compared with PCV13 serotype isolates (85 out of 104). Similarly, the proportion of isolates with ceftriaxone MIC ≤1.0 μg/mL was significantly greater ($P < .0001$) for non-PCV13 serotype isolates (334 out of 334) compared with PCV13 serotype isolates (93 out of 99). Serotype 19A isolates accounted for all but 2 of the isolates with penicillin MICs >2.0 μg/mL. All but 6 isolates

TABLE 5 Immune Evaluations of 28 Children With IPD Due to PCV13 Serotypes After Receiving ≥2 Doses of PCVs at 8 US Children's Hospitals

Immune Evaluations	No. Children Undergoing Testing
Quantitative immunoglobulins	26
IgG subclass	4
Humoral immune panel	17
Antibody to serotype causing IPD	15
Complement levels	13
T-cell studies	8
B-cell studies	6
Polymorphonuclear leukocyte studies	3
Mannose binding lectin	1
Antibody response to PPV23	2
HIV testing	2

Serotypes of isolates causing IPD in patients who had an immune evaluation: serotype 3 (n = 10), serotype 19A (n = 9), serotype 19F (n = 6), serotype 23F (n = 2), and serotype 14 (n = 1).

(all serotype 19A) in both groups combined had ceftriaxone MICs ≤1.0 μg/mL. For all isolates, 8.3% (36 out of 433) would be considered nonsusceptible to ceftriaxone for treating a central nervous system infection (17% [17 out of 99] for PCV13 serotype isolates versus 5.7% [19 out of 334] for non-PCV13 serotype isolates, $P < .001$).

DISCUSSION

In the United States, IPD in children has been markedly reduced because of the routine use of PCV7 beginning in 2000 followed by PCV13 in 2010. Most of the remaining cases are due to non-PCV13 serotypes. In 8 children's hospitals in the United States, we found that 4 to 7 years after PCV13 was introduced, ~25% of IPD cases in children were due to PCV13 serotype isolates, most commonly serotypes 3, 19A, and 19F. However, >40% of the children in our study who had IPD due to a PCV13 serotype isolate had received none or only 1 dose of PCV13 (or PCV7 if serotypes 14, 18C, 19F, or 23F) before their IPD.

Serotype 3 was the most common PCV13 serotype causing IPD in this study, but 42% (19 out of 45) of these patients had received none or only 1 dose of PCV13 before their IPD episode. In a study conducted by the Centers for Disease Control and Prevention and a recent systematic review and meta-analysis, it has been shown that the effectiveness of PCV13 is less for preventing IPD due to serotype 3 compared with serotypes 19A and 7F.[17,18] It has also been noted in other studies that PCV13 is less effective in preventing IPD due to serotype 3 compared with other PCV13 serotypes.[5,14,19] It is notable that only 2 of the patients in our study with IPD due to a serotype 3 isolate had an underlying condition. Serotype 19A was the second most common PCV13 serotype in this study, but >40% (12 out of 28) of these patients had received none or only 1 PCV13 dose. Others have reported serotype 19F among the more common PCV7 or PCV13 serotypes causing IPD or nasopharyngeal colonization in appropriately immunized children.[20–22] None of the 4 patients with IPD due to serotype 7F had received a dose of PCV13.

The most common non-PCV13 serotypes noted in our study were serotypes 35B, 23B, 33F, and 22F. Underlying conditions were noted in >50% of patients with non-PCV13 serotype IPD, which was significantly

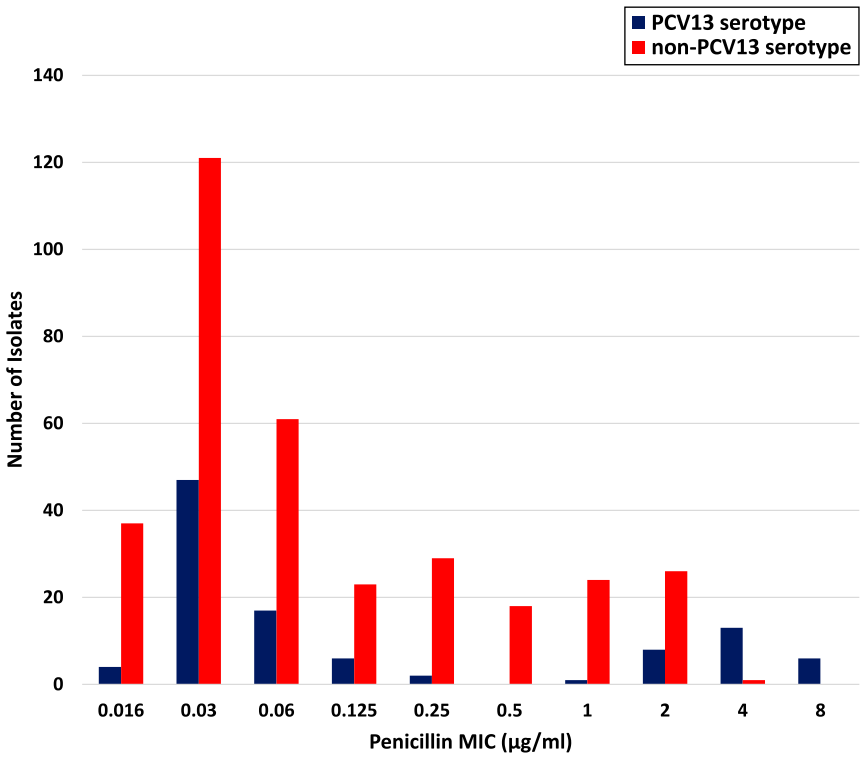

FIGURE 1
Penicillin MICs for PCV13 and non-PCV13 serotype isolates from 2014 to 2017. For noncentral nervous system infections, isolates were considered susceptible to parenteral penicillin if MICs were ≤2.0 μg/mL, and for central nervous system infections, isolates were considered susceptible to parenteral penicillin if MICs were ≤0.06 μg/mL.

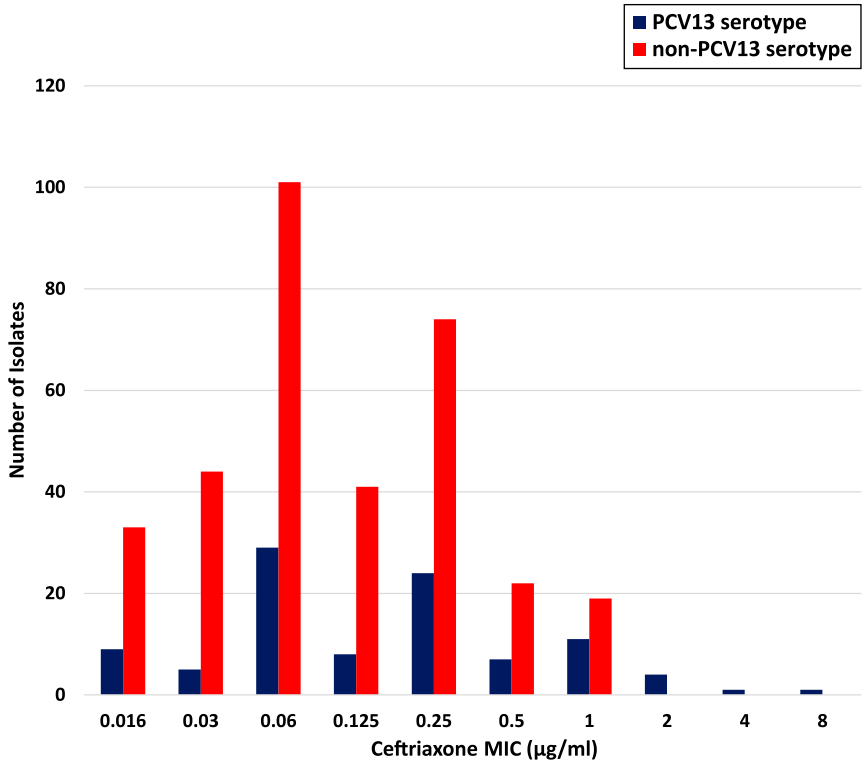

FIGURE 2

Ceftriaxone MICs for PCV13 and non-PCV13 serotype isolates from 2014 to 2017. For noncentral nervous system infections, isolates were considered susceptible to parenteral ceftriaxone if MICs were ≤1.0 µg/mL, and for central nervous system infections, isolates were considered susceptible for ceftriaxone if MICs were ≤0.5 µg/mL.

greater than the 23% of patients with underlying conditions and IPD caused by PCV13 serotype isolates. This may be related to the relatively decreased invasive potential of the non-PCV13 serotypes to cause IPD compared with PCV13 serotype isolates.[23] In the Active Bacterial Surveillance of IPD in the United States, the Centers for Disease Control and Prevention found that for children <5 years of age, the most common non-PCV13 serotypes for 2015–2016 were 23B, 22F, 33F, 15C, 15A, 35B, and 10A.[24] In Massachusetts children <18 years old, the most common non-PCV13 serotype isolates from April 2010 through March 2017 were 15BC, 33F, and 22F; PCV13 serotype isolates accounted for 33% of cases.[25] Other non-PCV13 serotype isolates are more common in reports from outside the United States; in addition, the relative frequency of the specific most common non-PCV13 serotypes from studies outside the United States differs from that noted in US studies.[26–28]

Although PCV13 serotype isolates were significantly more likely to be nonsusceptible to penicillin or ceftriaxone than non-PCV serotype isolates on the basis of the 2018 Clinical and Laboratory Standards Institute nonmeningeal site of infection interpretive breakpoints, still ~95% and 98% of all isolates were susceptible to penicillin or ceftriaxone, respectively. However, almost 10% of all isolates had ceftriaxone MICs considered nonsusceptible for treating central nervous system infections, which supports continuing to recommend the combination of ceftriaxone plus vancomycin for empirical treatment of suspected pneumococcal meningitis.[29]

Gaschignard et al[30] conducted a prospective study of children with IPD from 2005 to 2011 in 28 pediatric units in France. Of 163 patients (142 with meningitis) identified, 127 had complete and 35 had incomplete immunologic evaluations. Previous IPD had occurred in 17 patients, and 4 other patients had a history of other previous severe infections. Abnormal immunologic responses were found in 26 children (16%). Primary immune deficiencies were found more commonly in children >2 years of age (14 out of 53, 26%) compared with younger children (3 out of 109, 3%). The authors advocate for a systematic immunologic exploration for all children hospitalized for IPD. In a study from the United Kingdom, serum from 172 children with IPD submitted to the Health Protection Agency for measuring serotype-specific IgG antibody concentrations also had total serum IgG concentrations measured.[31] Nineteen (11%) had low IgG concentrations, although the levels were only marginally below the lower limit of normal for age. Three of the 19 children had a repeat IgG measurement 3 to 5 months later, and all 3 had IgG levels in the normal range, suggesting a transient IgG deficiency.

The 2015 American Academy of Pediatrics Red Book states that a child's HIV status and immunologic function should be considered for evaluation if they have IPD due to an isolate with a serotype in PCV13 and have received ≥2 doses of PCV13 at least 2 weeks before the onset of illness.[32] In our study, 28 children with IPD due to a PCV13 serotype isolate and who had received at least 2 doses of PCV13 (or PCV7 if a PCV7 serotype isolate caused IPD) had a full or partial immune evaluation at the discretion of their treating physicians. Only 1 patient was found to have a true immunodeficiency, and that patient had a strong family

history of CVID. It is of interest that this is the only patient who had meningitis despite 4 doses of PCV13. In our study, it is suggested that in an otherwise healthy child who has received ≥2 doses of PCV13 and subsequently develops IPD due to a PCV13 serotype isolate but without other evidence of an immunodeficiency from the history, physical examination, or routine laboratory studies, an immune evaluation is unlikely to be revealing. However, further studies are needed to determine the value of an immune evaluation for such patients.

Our study has several limitations. Not all information is available for all patients, including PCV administration. Some isolates were not available for testing. The serotypes of the isolates were not known in real time for most patients, and immune evaluations were done in only half of the children for whom this would be a consideration on the basis of the 2015 Red Book statement. Furthermore, the immune evaluations were not standardized, and many were composed primarily of quantitative immunoglobulin testing.

CONCLUSIONS

PCV13 serotypes (especially serotypes 3, 19A, and 19F) were responsible for 25% of IPD among children at 8 children's hospitals in the United States 4 to 7 years after the routine administration of PCV13 to infants was introduced. Almost 30% had not received any doses of PCV13 before the IPD episode, although >70% of these children were at an age at the time of the IPD at which they should have received ≥2 doses. Thus, additional cases of IPD might be prevented if PCV13 and PPSV23 are administered to all eligible children according to the recommended schedule. Considering >50% of the patients with non-PCV13 serotypes causing IPD had an underlying condition that could also be complicated by poor immune response to vaccination, further decreasing IPD in this group of children may be challenging. Finally, an immune evaluation for children who have IPD due to a PCV13 serotype isolate despite receiving ≥2 doses of PCV13 is unlikely to be helpful, unless other clinical information suggests an immunodeficiency.

ABBREVIATIONS

CVID: common variable immunodeficiency
IgG: immunoglobulin G
IPD: invasive pneumococcal disease
MIC: minimal inhibitory concentration
PCV: pneumococcal conjugate vaccine
PCV7: 7-valent pneumococcal conjugate vaccine
PCV13: 13-valent pneumococcal conjugate vaccine
PPSV23: 23-valent pneumococcal polysaccharide vaccine

Address correspondence to Sheldon L. Kaplan, MD, Texas Children's Hospital, Feigin Tower, Suite 1150, 1102 Bates Ave, Houston, TX 77030. E-mail: skaplan@bcm.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: No items to disclose other than the items listed in the Potential Conflict of Interest; the other authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Funded in part by a grant from Pfizer to Dr Kaplan.

POTENTIAL CONFLICT OF INTEREST: Dr Kaplan has provided unrelated consultant work for Pfizer. Dr Tan serves as an unpaid member of Pfizer's Data Safety and Monitoring Board. Dr Hulten has received unrelated travel support from Pfizer; the other authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

1. Kaplan SL, Barson WJ, Lin PL, et al. Early trends for invasive pneumococcal infections in children after the introduction of the 13-valent pneumococcal conjugate vaccine. *Pediatr Infect Dis J*. 2013;32(3):203–207
2. Moore MR, Link-Gelles R, Schaffner W, et al. Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: analysis of multisite, population-based surveillance. *Lancet Infect Dis*. 2015;15(3):301–309
3. Iroh Tam PY, Madoff LC, Coombes B, Pelton SI. Invasive pneumococcal disease after implementation of 13-valent conjugate vaccine. *Pediatrics*. 2014;134(2):210–217
4. Gaviria-Agudelo CL, Jordan-Villegas A, Garcia C, McCracken GH Jr. The effect of 13-valent pneumococcal conjugate vaccine on the serotype distribution and antibiotic resistance profiles in children with invasive pneumococcal disease. *J Pediatric Infect Dis Soc*. 2017; 6(3):253–259
5. Antachopoulos C, Tsolia MN, Tzanakaki G, et al. Parapneumonic pleural effusions caused by Streptococcus pneumoniae serotype 3 in children immunized with 13-valent conjugated

pneumococcal vaccine. *Pediatr Infect Dis J.* 2014;33(1):81–83

6. Madhi F, Godot C, Bidet P, et al. Serotype 3 pneumococcal pleural empyema in an immunocompetent child after 13-valent pneumococcal conjugate vaccine. *Pediatr Infect Dis J.* 2014;33(5):545–546
7. Angoulvant F, Levy C, Grimprel E, et al. Early impact of 13-valent pneumococcal conjugate vaccine on community-acquired pneumonia in children. *Clin Infect Dis.* 2014;58(7):918–924
8. Pírez MC, Algorta G, Chamorro F, et al. Changes in hospitalizations for pneumonia after universal vaccination with pneumococcal conjugate vaccines 7/13 valent and haemophilus influenzae type b conjugate vaccine in a Pediatric Referral Hospital in Uruguay. *Pediatr Infect Dis J.* 2014;33(7):753–759
9. Godot C, Levy C, Varon E, et al. Pneumococcal meningitis vaccine breakthroughs and failures after routine 7-valent and 13-valent pneumococcal conjugate vaccination in children in France. *Pediatr Infect Dis J.* 2015;34(10):e260–e263
10. Moraga-Llop F, Garcia-Garcia JJ, Díaz-Conradi A, et al. Vaccine failures in patients properly vaccinated with 13-valent pneumococcal conjugate vaccine in Catalonia, a region with low vaccination coverage. *Pediatr Infect Dis J.* 2016;35(4):460–463
11. Sütçü M, Aktürk H, Karagözlü F, et al. Empyema due to streptococcus pneumoniae serotype 9V in a child immunized with 13-valent conjugated pneumococcal vaccine. *Balkan Med J.* 2017;34(1):74–77
12. Diawara I, Zerouali K, Elmdaghri N, Abid A. A case report of parapneumonic pleural effusion caused by Streptococcus pneumoniae serotype 19A in a child immunized with 13-valent conjugate pneumococcal vaccine. *BMC Pediatr.* 2017;17(1):114
13. Yildirim I, Shea KM, Little BA, Silverio AL, Pelton SI; Members of the Massachusetts Department of Public Health. Vaccination, underlying comorbidities, and risk of invasive pneumococcal disease. *Pediatrics.* 2015;135(3):495–503
14. Oligbu G, Collins S, Andrews N, et al. Characteristics and serotype distribution of childhood cases of invasive pneumococcal disease following pneumococcal conjugate vaccination in England and Wales, 2006-2014. *Clin Infect Dis.* 2017;65(7):1191–1198
15. Kaplan SL, Mason EO Jr, Wald ER, et al. Decrease of invasive pneumococcal infections in children among 8 children's hospitals in the United States after the introduction of the 7-valent pneumococcal conjugate vaccine. *Pediatrics.* 2004;113(3 pt 1):443–449
16. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing,* 28th ed. Wayne, PA: Clinical and Laboratory Standards Institute; 2018
17. Wilson MR, Wasserman M, Jadavji T, et al. Response to McGirr et al.'s comment on "clinical and economic impact of a potential switch from 13-valent to 10-valent pneumococcal conjugate infant vaccination in Canada". *Infect Dis Ther.* 2018;7(4):539–543
18. Sings HL, De Wals P, Gessner BD, et al. Effectiveness of 13-valent pneumococcal conjugate vaccine against invasive disease caused by serotype 3 in children: a systematic review and meta-analysis of observational studies. *Clin Infect Dis.* 2019;68(12):2135–2143
19. Silva-Costa C, Brito MJ, Pinho MD, et al; Portuguese Group for the Study of Streptococcal Infections; Portuguese Study Group of Invasive Pneumococcal Disease of the Pediatric Infectious Disease Society. Pediatric complicated pneumonia caused by streptococcus pneumoniae serotype 3 in 13-valent pneumococcal conjugate vaccinees, Portugal, 2010-2015. *Emerg Infect Dis.* 2018;24(7):1307–1314
20. Park SY, Van Beneden CA, Pilishvili T, et al; Active Bacterial Core Surveillance Team. Invasive pneumococcal infections among vaccinated children in the United States. *J Pediatr.* 2010;156(3):478–483.e2
21. Oligbu G, Hsia Y, Folgori L, Collins S, Ladhani S. Pneumococcal conjugate vaccine failure in children: a systematic review of the literature. *Vaccine.* 2016;34(50):6126–6132
22. McFarland M, Szasz TP, Zhou JY, et al. Colonization with 19F and other pneumococcal conjugate vaccine serotypes in children in St. Louis, Missouri, USA. *Vaccine.* 2017;35(34):4389–4395
23. Yildirim I, Little BA, Finkelstein J, et al; T; he Massachusetts Dept. of Public Health. Surveillance of pneumococcal colonization and invasive pneumococcal disease reveals shift in prevalent carriage serotypes in Massachusetts' children to relatively low invasiveness. *Vaccine.* 2017;35(32):4002–4009
24. Matanock A. Invasive pneumococcal disease in the U.S.-2008-2016. Advisory Committee for Immnunization Practices October 26, 2017. Available at: https://pdfs.semanticscholar.org/34fc/5057868beb4b08c27a7c1e6f7f462c93f3ae.pdf. Accessed January 22, 2019
25. Yildirim I, Little B, Pelton SI. Invasive Pneumococcal Disease in Massachusetts Children 6 Years Following Introduction of PCV13 [Abstract 2493]. In: *Open Forum Infect Dis,* vol. 4. 2017:p S67
26. Ubukata K, Takata M, Morozumi M, et al; Invasive Pneumococcal Diseases Surveillance Study Group. Effects of pneumococcal conjugate vaccine on genotypic penicillin resistance and serotype changes, Japan, 2010-2017. *Emerg Infect Dis.* 2018;24(11):2010–2020
27. Jayasinghe S, Menzies R, Chiu C, et al. Long-term impact of a "3 + 0" schedule for 7- and 13-valent pneumococcal conjugate vaccines on invasive pneumococcal disease in Australia, 2002-2014. *Clin Infect Dis.* 2017;64(2):175–183
28. Waight PA, Andrews NJ, Ladhani NJ, et al. Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: an observational cohort study. *Lancet Infect Dis.* 2015;15(6):629
29. Olarte L. Vancomycin should be part of empiric therapy for suspected bacterial meningitis. *J Pediatric Infect Dis Soc.* 2019;8(2):187–188
30. Gaschignard J, Levy C, Chrabieh M, et al. Invasive pneumococcal disease in children can reveal a primary

immunodeficiency. *Clin Infect Dis*. 2014; 59(2):244–251

31. Stanford E, Ladhani S, Borrow R, et al. Immunoglobulin G deficiency in United Kingdom children with invasive pneumococcal disease. *Pediatr Infect Dis J*. 2011;30(6):462–465

32. American Academy of Pediatrics. Pneumococcal Infections. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*, 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:pp 626–638

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Invasive Pneumococcal Disease in Children's Hospitals: 2014–2017

Sheldon L. Kaplan, William J. Barson, Philana Ling Lin, José R. Romero, John S. Bradley, Tina Q. Tan, Pia S. Pannaraj, Laurence B. Givner and Kristina G. Hulten

Pediatrics 2019;144;
DOI: 10.1542/peds.2019-0567 originally published online August 16, 2019;