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Impact of Conjugated Pneumococcal Vaccines on Bacteremic Pneumococcal Pneumonia among Children in Massachusetts, 2002-2017

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Abstract

Impact of Conjugated Pneumococcal Vaccines on Bacteremic Pneumococcal

Pneumonia among Children in Massachusetts, 2002-2017

By Mohnd Elmontser

Introduction: *Streptococcus pneumoniae* is a major cause of community-acquired pneumonia at all ages. In 2010, a second-generation 13-valent pneumococcal conjugate vaccine (PCV13) replaced the 7-valent vaccine (PCV7) in the routine infant immunization program in the USA. The main aim of this study was to evaluate the effect of the PCV13 on bacteremic pneumococcal pneumonia among children in Massachusetts during 2010-2017.

Methods: A population-based enhanced passive surveillance for invasive pneumococcal disease (IPD) in children in the entire state of Massachusetts was initiated in October 2001. All clinical microbiology laboratories submit isolates of *S pneumoniae* from sterile body sites collected from Massachusetts residents < 18 years of age to the Massachusetts Department of Public Health (MDPH). Epidemiologists at the MDPH subsequently interview parents/guardians and/or primary care providers to obtain demographic and clinical information by using a standardized case report form.

Results: One-thousand-one-hundred-sixty-six cases of IPD were identified among children younger than 18 years of age between October,2001 and December,2017. Most of the cases (521, 44.6%) were under 2 years of age, 320 (27.4%) cases had at least one comorbidity and 310 (29.2%) were nonvaccinated. The most common clinical presentation was bacteremia (581, 49.8%) followed by bacteremic pneumonia (392, 33.6%). Prevalence of bacteremic pneumococcal pneumonia among IPD cases declined to 30.6% (106/346) in postPCV13-era from 34.9% (286/820) in prePCV13-era representing a 4.3% reduction ($p<0.05$). Serotypes 19A, 7F, 3, 6A, 22F, 4, and 33F were the most frequent serotypes in the prePCV13-era (37.8%, 21.5%, 6.0%, 4.6%, 3.7%, 3.2%, 2.8%, respectively) whereas in the postPCV13-era serotypes 19A, 22F, 7F, 3, 33F, 7C, 15A, and 15BC were the most frequent serotypes (16.3%, 11.9%, 7.6%, 5.4%, 4.3%, 4.3%, 4.3%, and 3.2% respectively). Penicillin resistance was found in 47.1% and 23.2% of isolates in pre and postPCV13-era respectively ($p<0.005$).

Conclusion: Sustained high vaccine coverage with PCV13 is expected to further reduce the burden of bacteremic pneumococcal pneumonia. Continued surveillance is critical to monitor trends of nonvaccine serotypes that might emerge to be highly associated with antibiotic resistance strains and the potential impact of new PCVs. In addition, appropriate antibiotic use remains essential to reducing rates of this problem.

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Background

Streptococcus pneumoniae is an important bacterial pathogen that causes a variety of clinical manifestations, such as meningitis, septicemia, and pneumonia; resulting in nearly one million global childhood deaths annually. Pneumococcal pneumonia is a leading cause of morbidity and mortality and has a high disease burden, with an estimated 826,000 annual deaths globally in children one month to five years of age (1). *S. pneumoniae* is the main cause of community-acquired pneumonia and meningitis at all ages. Invasive disease states are seen more often in those in extreme age groups and in those with comorbidities (2).

There are more than 98 different serotypes of *S. pneumoniae* based on polysaccharide capsules that differ in their ability to protect the organism from opsonophagocytic killing (3). Before the year 2000, the only pneumococcal vaccine available commercially was a 23-valent capsular polysaccharide vaccine (PPSV23). The vaccine has been shown to be effective against invasive pneumococcal disease (IPD) in adults, but antibody response in children younger than two years of age is poor (4).

Pneumococcal conjugated vaccines (PCVs) prevent acquisition and carriage of vaccine serotypes in the nasopharynx and impede a key step in the pathogenesis of pneumococcal disease. In 2000, introduction of PCV7 has dramatically reduced the incidence of invasive disease caused by vaccine serotypes, both in vaccinated young children and unvaccinated groups, due to indirect protection wherever high vaccine uptake in the pediatric population has been achieved (5) (6).

In 2010, a second-generation pneumococcal conjugate vaccine (PCV13; Prevnar-13, Pfizer, NY. USA) replaced PCV7 for use in the routine infant immunization program

in the USA. Three PCVs are currently available on the global market: PCV7, 10-valent (PCV10), and PCV13, and were licensed in 2000, 2008 and 2009, respectively (7). PCV7 contains polysaccharides from the seven most common invasive pneumococcal strains that were seen in North America before 2000 i.e. serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, conjugated to a nontoxic diphtheria-toxin analog (CRM197). The second-generation PCV, PCV13 used PCV7 as a base, but included additional serotypes i.e. 1, 3, 5, 6A, 7F and 19A conjugated to CRM197 (4).

Globally, antimicrobial resistance among pneumococci spread rapidly in the 1990s, reflecting dissemination of new strains (8). Implementation and widespread use of conjugated vaccines not only decreased the incidence of invasive disease but also contributed to the reductions in disease due to mostly resistant serotypes. The most common serotypes responsible for the invasive disease were also the serotypes that harbored resistance genes before the first generation PCV i.e. 18C, 19F. Therefore, PCV7 caused reduction in antibiotic resistance via directly targeting antibiotic-resistant strains causing disease in children as well as reduction in prescription of antibiotics due reduction in febrile illnesses that often lead to the use of antibiotics. The incidence of resistance varies substantially among different geographic regions and is influenced by patterns of population density, antibiotic use, and local prevalence of strains (8). The use of specific antibiotic classes not only creates predisposition for resistance to that class but also may facilitate emergence of resistance to unrelated antibiotic classes (2). These findings highlight the importance of continuing the search for a better pneumococcal vaccine and demonstrating the effectiveness of the current PCVs to provide protection, specifically against bacteremic pneumococcal pneumonia in children.

Methods

A population-based surveillance for *S pneumoniae* infection in children was initiated in Massachusetts in October 2001. All clinical microbiology laboratories in Massachusetts submit isolates of *S pneumoniae* from blood, cerebrospinal fluid, or other normally sterile body sites collected from Massachusetts residents < 18 years of age to the Massachusetts Department of Public Health (MDPH). Epidemiologists at the MDPH subsequently interview parents/guardians and/or primary care providers to obtain demographic and clinical information, including underlying comorbidities, about each case by using a standardized case report form.

The current study was restricted to IPD cases identified after April 1, 2002, and study years were defined as the 12-month period from April 1 of the first year until March 31 of the following year to examine the impact of PCV13 implementation on bacteremic pneumococcal pneumonia among children in Massachusetts, 2002-2017.

Vaccination status was defined in two categories. A child was presumed to have complete vaccination if the child had received an adequate number of PCV immunizations to have had a protective immune response against the vaccine serotypes at least 14 days before the diagnosis of IPD. Otherwise, a child was categorized as having incomplete vaccination. Adequate number of immunizations for children <12 months of age was defined as two or more PCV doses. Children who received zero or one PCV dose were presumed to have incomplete vaccinations. For children 12 months of age or older, complete vaccination required at least one PCV dose after the age of 12 months; otherwise, they were considered to have incomplete vaccination.

The presence of *S. pneumoniae* was confirmed by optochin sensitivity (≥ 5 mm inhibition) and bile solubility by using standard microbiologic methods according to guidelines from the Clinical and Laboratory Standards Institute and serotyped by Quelling reaction by using pneumococcal antisera (Statens Serum Institute, Copenhagen, Denmark). Serotypes were classified as follows: PCV7 included serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F; PCV13 included the serotypes found in PCV7 and serotypes 1, 3, 5, 7F, 6A, and 19A; PPV23 included the serotypes found in PCV7 and serotypes 1, 2, 3, 5, 7F, 8, 9N, 10A, 11A, 12F, 15B, 17F, 19A, 20, 22F, and 33F.

Antibiotic susceptibility to penicillin, ceftriaxone, azithromycin, and trimethoprim/sulfamethoxazole was determined by E-tests (BioMerieux, Durham, NC), according to manufacturer guidelines, and minimum inhibitory concentration (MIC) interpretations were based on the Clinical and Laboratory Standards Institute 2012 guidelines.

We used measures of central tendency (mean, median) and dispersion (standard deviation and 95% confidence intervals [95%CI] of the mean, and interquartile range [IQR] around the median) for continuous variables, and frequency distributions (number, percentage) for categorical scale variables. Differences in mean/median of continuous variables was tested with the 2-sided t test or a nonparametric Mann-Whitney test when appropriate. Categorical variables were compared between groups using $\chi 2$ test or Fisher exact test if there are <5 observations in one group. Statistical analyses were conducted in SAS version 9.4 software (SAS Inc. Cary, NC).

Results

One-thousand-one-hundred-sixty-six cases of IPD were identified among children younger than 18 years of age between October 2001 and December 2017. There were 127 (11.0%) cases in infants <6 months; 154 (13.2%) in infants between 6-12 months; 240 (21.0%) in children 12-24 months; 330 (28.3%) in children aged 2-5 years, and 315 (27.0%) were in children aged >5 years. 521 (44.6%) were under 2 years of age (Table 1). There were 693 (58.9%) male and 521 (45.0%) Caucasian.

Clinical Presentations: Bacteremia was the most frequent presentation and was reported in about half of all IPD cases (581, 49.8%) followed by pneumonia (392, 33.6%) (Table 1). There were 84 (7.2%) meningitis cases. Prevalence of bacteremic pneumococcal pneumonia among IPD cases declined to 30.6% (106/346 children) in postPCV13 period from 34.9% (286/820 children) which represents a 4.3% reduction ($p < 0.05$) (Table 1, Figure 1).

Comorbidities: Information on comorbidities was available for 1090 (93.4%) of 1166 children. Of these, 320 (27.4%) cases were identified to have at least one underlying clinical condition (Table 1). The most common conditions included immunosuppression due to organ transplant (34.4%, 10/29), and hematologic malignancy (27.5%, 8/29) (Table 2).

Immunization status: There were 570 (53.6%) patients who were fully vaccinated, 310 (29.2%) were nonvaccinated. Data regarding vaccination were not available for 182 (17.1%) of 1166 children. Pneumonia due to PCV7 serotypes or PCV7–related serotypes (13 of 73 serotyped cases; 17.8%) was only found in the group of nonvaccinated children. After PCV13 implementation, the proportion of nonvaccinated

children among IPD cases increased compared to prePCV13 period (18.0% in prePCV13 and 53.0% in postPCV13 era, $p < 0.05$) (Table 1).

Serotype distribution: Serotype information was available for 392 (100%) cases with bacteremic pneumococcal pneumonia (Table 3). Serotypes 19A, 7F, 3, 6A, 22F, 4, and 33F were the most frequent serotypes in the prePCV13 era (37.8%, 21.5%, 6.0%, 4.6%, 3.7%, 3.2%, and 2.8%, respectively) whereas in the postPCV13 era serotypes 19A, 22F, 7F, 3, 33F, 7C, 15A, and 15BC were the most frequent serotypes (16.3%, 11.9%, 7.6%, 5.4%, 4.3%, 4.3%, 4.3%, and 3.2% respectively) (Figures 2 and 3).

Susceptibility: Results for antibiotic susceptibility testing were available for 309 (78.8%) of 392 isolates obtained from bacteremic pneumonia cases (Table 4). The prevalence of drug-resistant *S pneumoniae* declined dramatically after PCV13 implementation (Figure 4). Penicillin non-susceptibility was found in 102 (47.1%) and 31 (23.2%) of isolates in pre and postPCV13 era respectively ($p <0.005$) (Table 4). When CNS breakpoints were used 21 (9.7%) and 5 (5.3%) were penicillin non-susceptible in pre and postPCV13 era respectively ($p <0.005$) (Table 4).

Discussion

Our study uses a unique data set that includes pneumococcal isolates from state-wide IPD cases from children across Massachusetts younger than 18 years old starting after the implementation of the first-generation PCV. These data, coming from an ongoing surveillance system over a 15-year time period, enabled us to compare the proportion of bacteremic pneumococcal pneumonia cases in a state with sustained high vaccine coverage between 2002 – 2017, postPCV vaccine implementation. It allowed us to describe the serotype distribution of bacteremic pneumococcal pneumonia over 15 years in order to gain further insight into our understanding of vaccine serotypes (VSTs) and prevalent non-vaccine serotypes (NVSTs) that have emerged in the postPCV era. Extensive laboratory data allowed us to describe the susceptibility patterns for bacteremic pneumococcal pneumonia causing *S. pneumoniae* isolates.

The results of our study should be assessed in the context of dramatic and sustained decline of bacteremic pneumococcal pneumonia in children in the setting where PCV13 was implemented. The findings were driven largely by the effectiveness of PCV13 against serotypes: 1, 3, 5, 6A, 7F and 19A. These serotypes were responsible for 53.6 % of S. *pneumoniae* associated illnesses among children across Massachusetts younger than 18 years before PCV13 introduction.

The effectiveness of pneumococcal conjugate vaccines is well recognized through a rapid and substantial reduction of overall IPD rates in children and adults (9). However, the clinical presentation and outcomes of remaining cases of IPD have evolved. In the post PCV era, a higher proportion of children with IPD are admitted to hospital due to more severe disease manifestations (10). This raises the question of whether the changes in the nature and severity of IPD after PCVs implementation, as a result of

changes in serotype distribution with higher prevalence of NVST, could have led to higher severity of disease in the population, as indicated by other studies. If this increase continues, it is possible that the maximum benefit of the PCV13 vaccine in children will have already been achieved; indicating that new strategies will be needed to prevent further cases of *S pneumoniae*. Some researchers have suggested that PCVs may be more effective at preventing IPD in children without underlying comorbidities, in whom less severe disease may occur (11) (12).

There was a significant decrease in the incidence of IPD caused by all serotypes and this incidence fell markedly in children aged <24 months. Similar to our study, other studies also observed a significant reduction in presenting children aged less than two years old after PCV13's introduction (13). This is important for understanding what age groups to target for vaccination in the future.

While the PCV13 vaccine has been effective in reducing the overall incidence of IPD in children since its introduction to the US childhood vaccination program, the results from our study suggest that in the post-vaccine period, IPD continues to cause mortality in children. Although the prevalence of pneumonia among children who presented with invasive pneumococcal disease has significantly decreased, the proportion of cases resulting in death has increased since the introduction of PCV13.

Its different serotype composition may contribute positively to PCV13's demonstrated effectiveness. Our results show the effectiveness of PCV13 in preventing pneumonia was especially high for serotypes 19A and 7F comparing with other serotypes. Furthermore, this PCV contains serotype 19A and 3, which are not included in previous PCVs and are two of the most common causes of severe pneumonia and empyema (14).

Antibiotic-non-susceptible *S. pneumoniae* complicates the treatment of pneumococcal disease and has been associated with worse clinical outcomes (15). Our study focused on the impact of high PCV13 vaccine coverage on antibiotic-non-susceptibility in bacteremic pneumococcal pneumonia in children, during the post PCV13 period. After PCV13's introduction, antibiotic-non-susceptible IPD decreased in children less than 18 years old. This finding shows that reductions in resistance can be achieved rapidly for certain bacteria with an effective vaccine; a finding similar to the experience with PCV7 (16).

This study has several limitations. First, although we used an ongoing surveillance that extends over almost two decades, our predictions are limited by the number of data points. Number of variables and the performance of our models depend on available data. Data were analyzed retrospectively, and the quality of data relies on the data collection process including accuracy of collected information using case report forms. Our results may not be generalized to the settings with lower vaccine coverage where indirect protection from PCVs will be different. In Massachusetts where vaccine coverage rates are approximately >95%, risk of exposure to and transmission of vaccine serotypes from unvaccinated children will be lower compared to settings with more unvaccinated children who can be colonized with serotypes included in the PCVs. Potential confounders collected during the parent interview and from medical providers included demographic and clinical information, vaccination history, immunocompromising disorders, and other underlying comorbidities, which did not allow us to control over other potential confounders.

Conclusions

We recommend sustained high PCV13 coverage to continue in order to further reduce bacteremic pneumococcal pneumonia. Continued surveillance is critical to monitor trends of non-vaccine serotypes that might emerge to be highly associated with antibiotic resistance strains and the potential impact of new PCVs. In addition, appropriate antibiotic use remains essential to reduce the expansion of antibiotic resistance.

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Tables and Figures

Table 1. Selected characteristics of children with IPD by age group over 15 years post PCV era, Massachusetts, USA

Characteristics		Before PCV13 (N=820), n (%)	After PVC13 (N=346), n (%)	Total (N=1166), n (%)	p-value
Gender	Male	479 (58.5)	208 (60.5)	693 (58.93)	0.5310^
	Female	340 (41.5)	136 (39.5)	483 (41.07)	
Race	Caucasian	373 (46.0)	148 (43.0)	521 (45.0)	<0.0001^
	Black	83 (10.1)	45 (13.0)	128 (11.0)	
	Asian	36 (4.4)	23 (7.0)	59 (5.1)	
	Hispanic	109 (13.3)	25 (7.2)	134 (11.5)	
	Unknown	183 (22.3)	61 (18.0)	244 (21.0)	
	Other	36 (4.4)	44 (13.0)	80 (7.0)	
Age (mo)	0 - <6mo	91 (11.1)	36 (10.4)	127 (11.0)	<0.0001^
	6 - <12 mo	112 (14.0)	42 (12.1)	154 (13.2)	
	12 - <24 mo	179 (22.0)	61 (18.0)	240 (21.0)	
	24 - 60 mo	229 (28.0)	101 (29.2)	330 (28.3)	
	≥ 60 mo	209 (26.0)	106 (31.0)	315 (27.0)	
Clinical syndrome	Bacteremia	384 (47.0)	197 (56.9)	581 (49.8)	0.0092^
	Pneumonia	286 (34.9)	106 (30.6)	392 (33.6)	
	Meningitis	64 (7.8)	20 (5.8)	84 (7.2)	
	Others	86 (10.5)	23 (6.7)	21 (9.4)	
Comorbidity	Yes	225 (27.4)	95 (27.4)	320 (27.4)	<0.0001^
	No	559 (68.1)	211 (60.9)	770 (66.0)	
	Unknown	36 (4.3)	40 (11.5)	76 (6.5)	
Immunization status	Vaccinated	410 (57.3)	160 (46.3)	570 (53.6)	<0.0001*
	Unvaccinated	128 (18.0)	182 (53.0)	310 (29.2)	
	Unknown	178 (25.0)	4 (1.2)	182 (17.1)	
Outcome	Died	15 (1.8)	15 (4.3)	30 (2.7)	<0.0001^
	Recovered	766 (93.4)	295 (85.3)	1061 (91.0)	
	Unknown	39 (4.8)	36 (10.4)	75 (6.4)	

^ Chi-Square test, * Fisher's Exact Test, mo months

Table 2. Underlying comorbidities among bacteremic pneumococcal pneumonia cases over 15 years post PCV era, Massachusetts, USA

Comorbidity	<24 month-old (n=24)		24-60 month-old (n=34)		>60 month-old (n=44)		Total (n=102)*	
	n	%	n	%	n	%	n	%
Sickle cell disease	1	4.17	5	8.8	3	13.6	9	8.8
Prematurity/LBW	6	25	4	11.7	1	2.2	11	10.7
Chronic Respiratory Disease	5	20.7	7	20.5	13	29.5	24	24.4
Asthma	4	16.6	6	17.6	11	25	21	20.5
CLD	1	4.1	1	2.9	2	4.5	4	3.9
GI disease	3	2.2	0	0	0	0	3	0.9
Biliary atresia	1	4.1	0	0	0	0	1	0.9
Other GI	0	0	0	0	0	0	0	0
Cong heart disease	6	24.9	4	11.7	1	2.2	11	10.7
Diabetes	0	0	0	0	1	2.2	1	0.9
Immunosuppression	2	8.2	8	23.4	19	42.8	29	28.1
Hematologic malignancy	0	0	4	11.7	4	9	8	7.8
Transplant	1	4.1	3	8.8	6	13.6	10	9.8
Rheum dis on steroids	0	0	0	0	2	4.5	2	1.9
Nephrotic syndrome	0	0	1	2.9	2	4.5	3	2.9
Hematologic disease on steroids	0	0	0	0	2	4.5	2	1.9
Immunocompromised**	1	4.1	0	0	1	2.2	2	1.9
Primary immunodeficiency	0	0	0	0	2	4.5	2	1.9
Neuromuscular disorders/seizure	3	12.5	6	17.6	5	11.3	14	13.7
Cochlear implant	0	0	0	0	1	2.2	1	0.9
Total	24	100	34	100	44	100	102	100

CLD chronic lung disease, LBW low birth weight, GI gastrointestinal system, CSF cerebrospinal fluid, Rheum rheumatological. * Only children with specified clinical condition. ** Includes children with HIV, rheumatological diseases with immunosuppressive treatment

Figure 1 Distribution of bacteremic pneumococcal pneumonia cases over years among children in Massachusetts who presented with invasive pneumococcal disease, 2002-2017

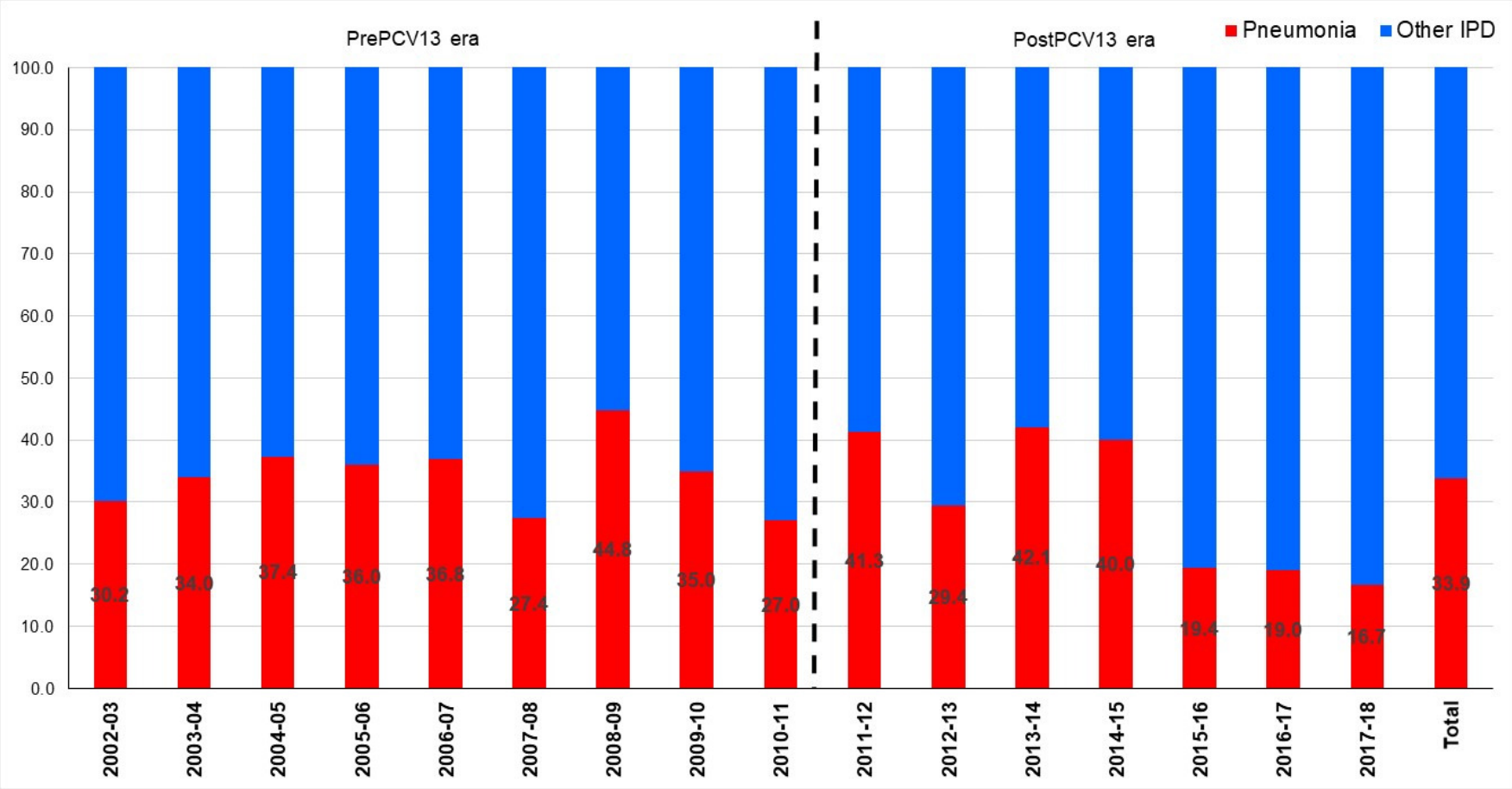


Table 3. Distribution of serotypes isolated from bacteremic pneumococcal pneumonia cases by vaccine groups among children in Massachusetts before and after implementation of PCV13

Serotypes	PrePCV13		PostPCV13	
	N	%	N	%
PCV7 serotypes	23	8.0	3	2.8
+6 in PCV13	154	53.8	38	35.8
+11 in PPSV23	20	6.9	25	23.5
NVST	89	31.1	40	37.7
Total	286	100.0	106	100.0

PCV7 7-valent pneumococcal conjugate vaccine, PCV13 13-valent pneumococcal conjugate vaccine, PPSV23 23-valent Pneumococcal Polysaccharide Vaccine, NVST Non-Vaccine Serotypes.

Figure 2 Distribution of bacteremic pneumococcal cases by serotypes over years among children in Massachusetts, 2002-2017

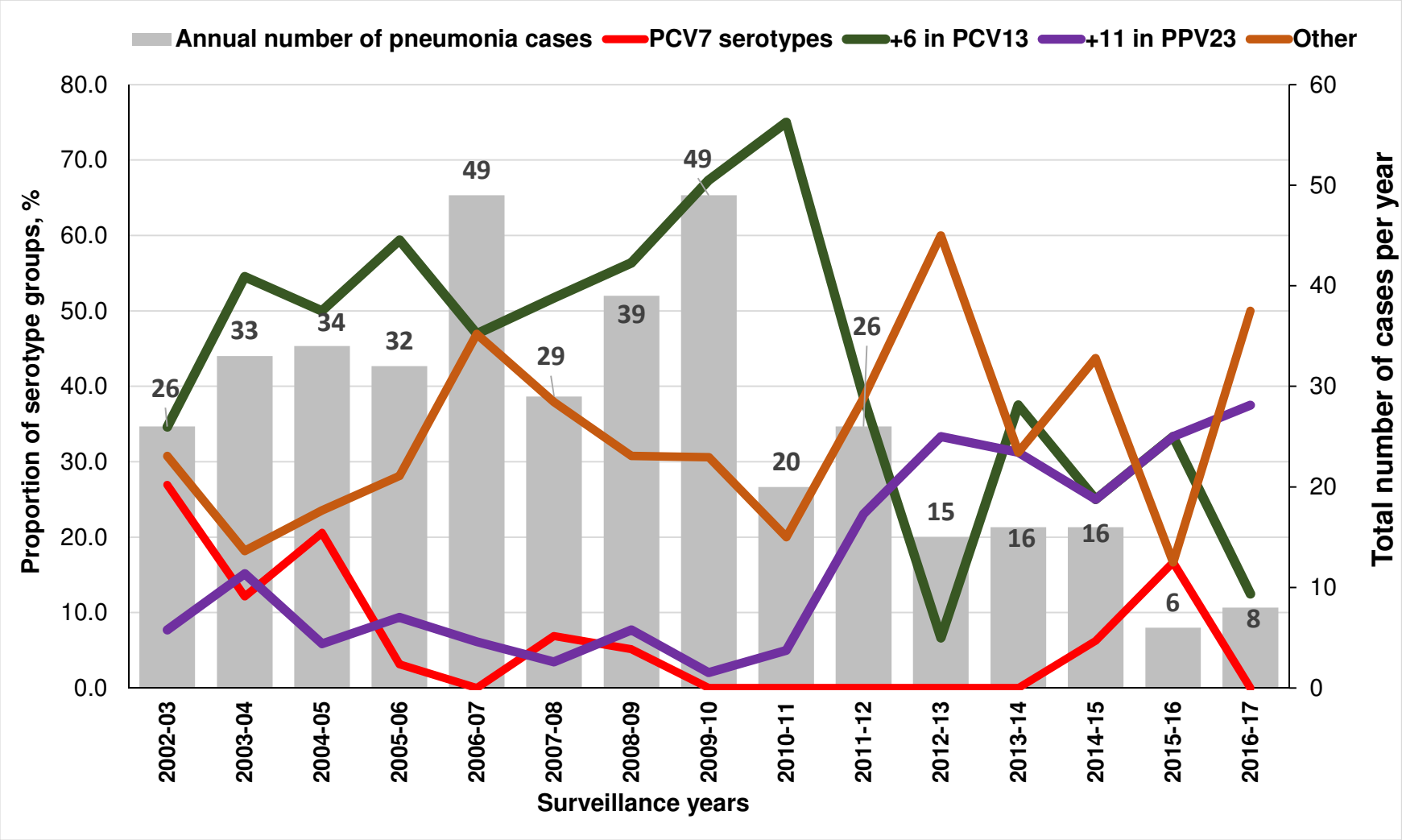


Figure 3. Serotypes causing bacteremic pneumococcal pneumonia among children in Massachusetts before and after implementation of PCV13

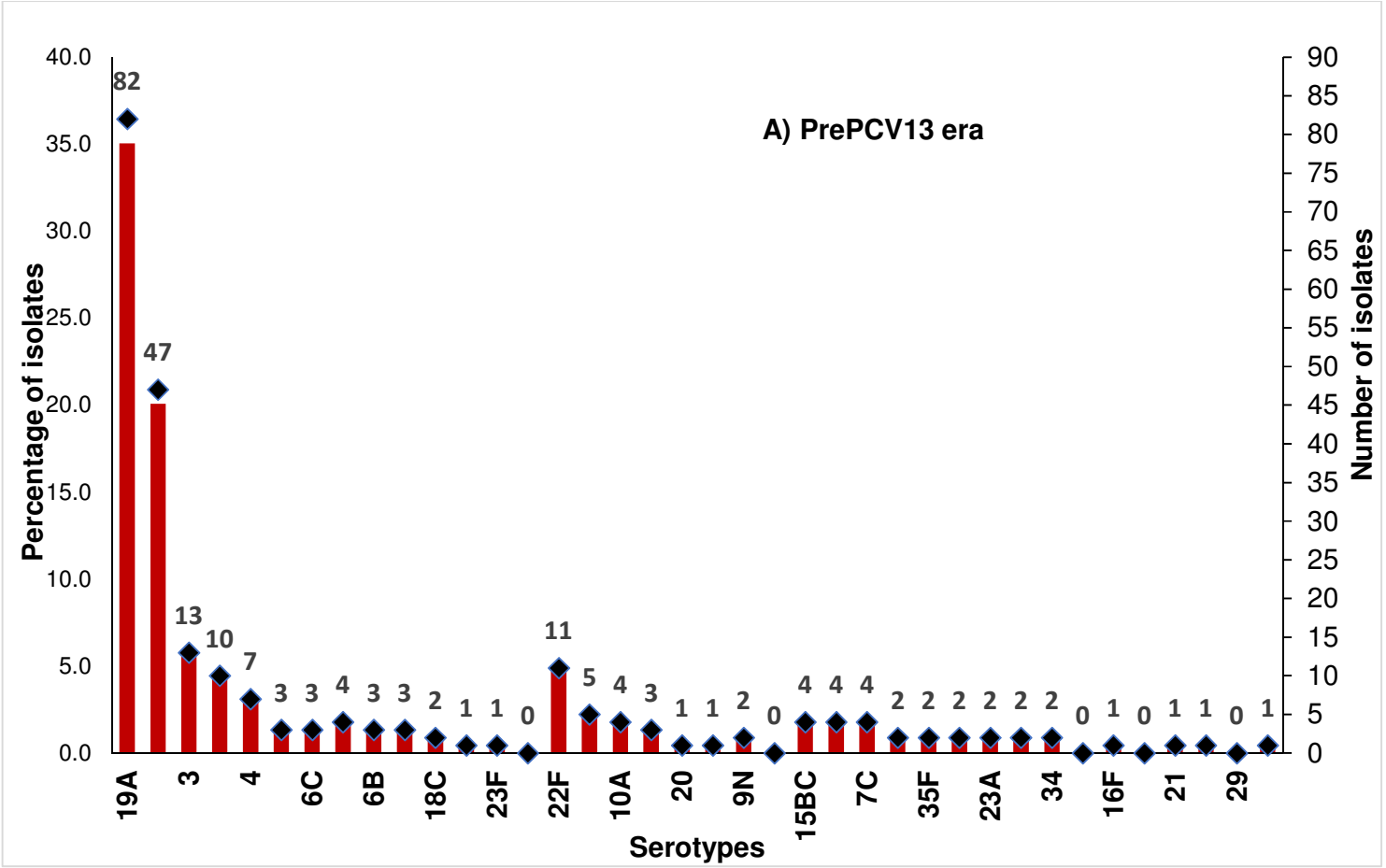


Figure 3. Serotypes causing bacteremic pneumococcal pneumonia among children in Massachusetts before and after implementation of PCV13 (continued)

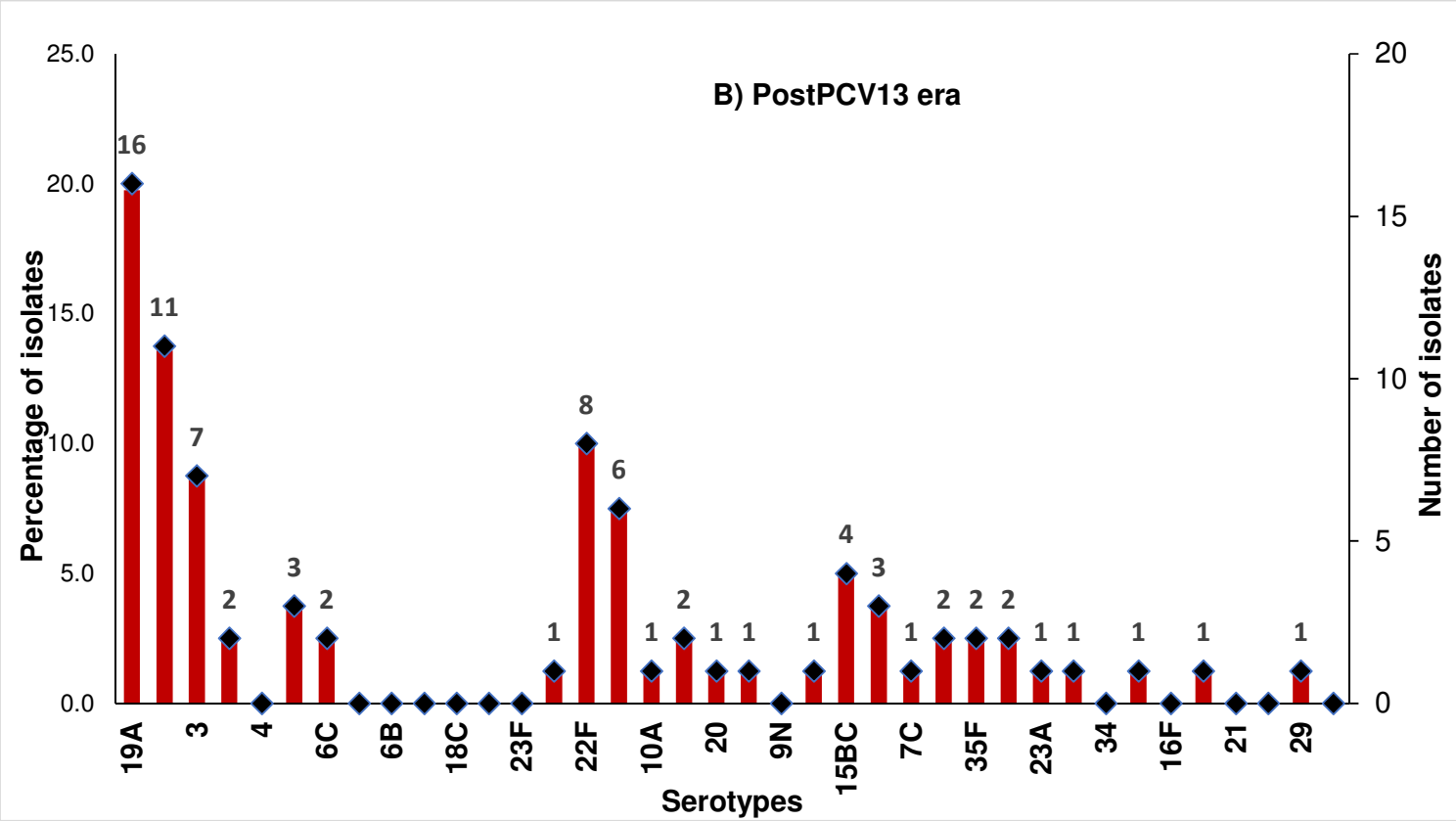
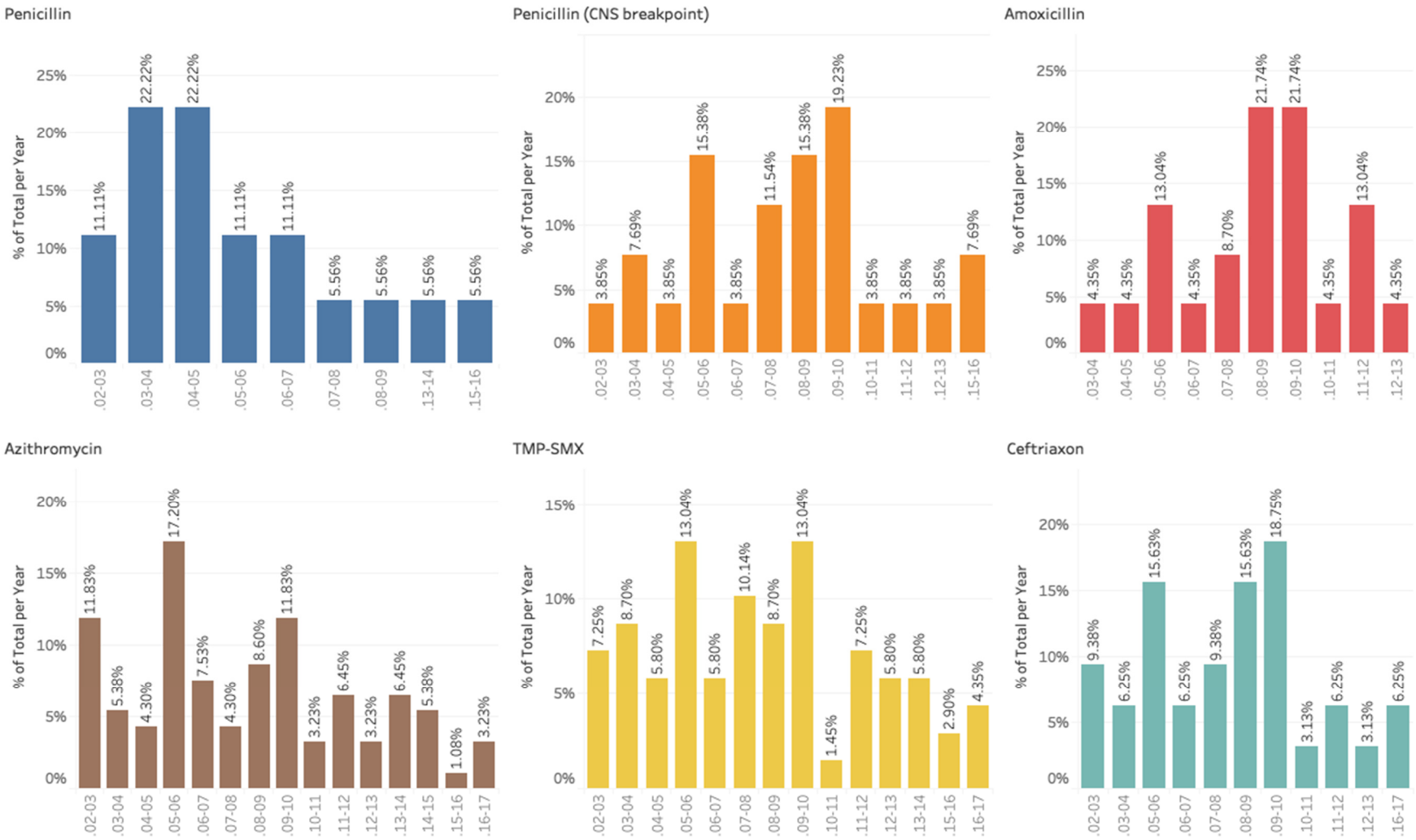


Table 4. Susceptibility patterns for *Streptococcus pneumoniae* isolates from bacteremic pneumococcal pneumonia in children over 15 years post PCV era, Massachusetts, USA

		Before PCV13 (N=216), n (%)	After PVC13 (N=93), n (%)	Total (N=309), n (%)	p-value
Penicillin	Susceptible	114 (52.7)	62 (66.6)	176 (56.9)	0.005^
	Resistant, Int.	79 (36.5)	26 (27.9)	105 (33.9)	
	Resistant, High	23 (10.6)	5 (5.3)	28 (9.1)	
Penicillin (CNS breakpoint)	Susceptible	195 (90.2)	88 (94.6)	283 (91.5)	0.008^
	Resistant, Int.	19 (8.8)	3 (3.2)	22 (7.1)	
	Resistant, High	2 (0.9)	2 (2.1)	4 (1.29)	
Amoxicillin	Susceptible	198 (91.6)	88 (94.6)	286 (92.5)	0.017^
	Resistant	18 (8.3)	5 (5.3)	23 (7.4)	
Ceftriaxone	Susceptible	190 (87.9)	87 (93.5)	277 (89.6)	0.019^
	Resistant, Int.	9 (4.1)	3 (3.2)	12 (3.8)	
	Resistant, High	17 (7.8)	3 (3.2)	20 (6.4)	
Azithromycin	Susceptible	150 (69.4)	66 (70.9)	216 (69.9)	0.025^
	Resistant	66 (30.5)	27 (29.0)	93 (30.1)	
TMP-SMX	Susceptible	166 (76.8)	74 (79.5)	240 (77.6)	0.019^
	Resistant, Int.	24 (11.1)	13 (13.9)	37 (11.9)	
	Resistant, High	26 (12.0)	6 (6.4)	32 (10.3)	

^ Fisher's Exact test, TMP-SMX Trimethoprim-Sulfamethoxazole

Figure 4. Antibiotic Susceptibility Trends Over Years among Pneumonia Cases



Intermediate and resistant isolates were merged as one category.