

UC Irvine

UC Irvine Previously Published Works

Title

Impact of 13-Valent Pneumococcal Conjugate Vaccination on Streptococcus pneumoniae Carriage in Young Children in Massachusetts

Permalink

<https://escholarship.org/uc/item/23b126f8>

Journal

Journal of the Pediatric Infectious Diseases Society, 3(1)

ISSN

2048-7193

Authors

Lee, Grace M
Kleinman, Ken
Pelton, Stephen I
[et al.](#)

Publication Date

2014-03-01

DOI

10.1093/jpids/pit057

Peer reviewed

Impact of 13-Valent Pneumococcal Conjugate Vaccination on *Streptococcus pneumoniae* Carriage in Young Children in Massachusetts

Grace M. Lee,^{1,2} Ken Kleinman,¹ Stephen I. Pelton,³ William Hanage,⁴ Susan S. Huang,⁵ Matthew Lakoma,¹ Maya Dutta-Linn,¹ Nicholas J. Croucher,⁴ Abbie Stevenson,⁴ and Jonathan A. Finkelstein^{1,6}

¹Center for Child Health Care Studies, Department of Population Medicine, Harvard Pilgrim Health Care Institute and Harvard Medical School, ²Division of Infectious Diseases and Department of Laboratory Medicine, Boston Children's Hospital, ³Department of Pediatrics, Boston University School of Medicine, and ⁴Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts; ⁵Division of Infectious Diseases, University of California Irvine; and ⁶Department of Medicine, Boston Children's Hospital, Massachusetts

Corresponding Author: Grace M. Lee, MD, MPH, Department of Population Medicine, 133 Brookline Ave, 6th Fl, Boston, MA 02215. E-mail: grace.lee@childrens.harvard.edu.

Received April 1, 2013; accepted June 22, 2013; electronically published October 3, 2013.

Background. In April 2010, a 13-valent pneumococcal conjugate vaccine (PCV13) replaced PCV7 for use in the United States. We evaluated rates of pneumococcal colonization, by serotype and antibiotic resistance, in Massachusetts communities where serial cross-sectional surveillance has been conducted for the past decade. **Methods.** Nasopharyngeal swabs were obtained from children 0 to <7 years of age and seen by primary care providers for well child or acute illness visits in 2001, 2004, 2007, 2009, and 2011. Pneumococcal isolates were serotyped by Quellung reaction and classified as PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F), additional PCV13 serotypes (1, 3, 5, 6A, 7F, 19A), or non-PCV13 serotypes. Changes in colonization and impact of PCV13 were assessed using generalized linear mixed models, adjusting for known risk factors and accounting for clustering by community. **Results.** Introduction of PCV13 did not affect the rate of overall pneumococcal colonization (31% in 2011). Colonization with non-PCV13 serotypes increased between 2001 and 2011 for all children (odds ratio [OR] per year, 1.12; 95% confidence interval [CI], 1.10, 1.15; $P < .0001$). 19A remained the second most common serotype in 2011, although a decline from 2009 was observed. Penicillin (7%), erythromycin (28%), ceftriaxone (10%), and clindamycin (10%) nonsusceptibility were commonly identified, concentrated among a small number of serotypes (including 19A, 35B, 15B/C, and 15A). Among healthy children 6–23 months old, colonization with PCV13 serotypes was lower among recipients of PCV13 vaccine (adjusted OR, 0.30; 95% CI, 0.11, 0.78). This effect was not observed in 6- to 23-month-old children with a concomitant respiratory tract infection (adjusted OR 1.36; 95% CI, 0.66, 2.77) or children 2 to <7 years old (adjusted OR, 1.17; 95% CI, 0.58, 2.34). **Conclusions.** 13-Valent pneumococcal conjugate vaccine reduced the prevalence of colonization with PCV13 serotypes among children 6–23 months old, but its efficacy was not shown among older children.

Key words. colonization; pneumococcal conjugate vaccine; *Streptococcus pneumoniae*.

BACKGROUND

After the introduction of universal immunization of children less than 2 years of age with 7-valent pneumococcal conjugate vaccine (PCV7) in 2000, the United States has witnessed dramatic declines in nasopharyngeal colonization and invasive pneumococcal disease (IPD) due to PCV7 serotypes [1–9]. Despite unchanged pneumococcal colonization rates and virtually complete serotype replacement in carriage, IPD caused

by non-PCV7 strains has increased only modestly. Our previous studies of colonization demonstrated a stable equilibrium among young children in Massachusetts by 2007, with 19A, 15B/C, and 6C emerging as predominant carriage serotypes in surveillance studies [7, 10].

In February 2010, a PCV13 was licensed in the United States and subsequently replaced PCV7 for universal use in infants and children through 5 years of age [11]. 13-Valent

pneumococcal conjugate vaccine includes 6 capsular antigens of *Streptococcus pneumoniae* serotypes 1, 3, 5, 6A, 7F, and 19A in addition to the serotypes included in PCV7 (4, 6B, 9V, 14, 18C, 19F and 23F) [11, 12]. 13-Valent pneumococcal conjugate vaccine was predicted to further reduce the prevalence of both carriage and IPD due to these additional serotypes, particularly 19A given its high prevalence among young children and its association with antibiotic resistance [3, 4, 13, 14].

We have been conducting serial cross-sectional surveillance of pneumococcal carriage since 2001 in selected Massachusetts communities [6, 7, 9, 16]. In this study, we describe the epidemiology of pneumococcal carriage in young, healthy children by serotype and by antibiotic resistance in the post-PCV7 (2000–2001, 2003–2004), pre-PCV13 (2006–2007, 2008–2009), and post-PCV13 (2010–2011) periods. To evaluate the early impact of PCV13 vaccination on carriage rates, we compare the risk for colonization among children who were and were not vaccinated with PCV13.

METHODS

Study Design and Population

Our study population comprised children <7 years of age seen for well child or acute care visits in 16 Massachusetts communities in 2000–2001 and 2003–2004, 9 communities in 2006–2007, 8 communities in 2008–2009, and 9 communities in 2010–2011 [6, 7, 9, 16]. The initial 16 communities (all outside of metropolitan Boston) were chosen for geographic separation. Starting in 2006–2007, surveillance was continued in 8 of these 16 communities. At the same time, one site (Boston Medical Center) was added to include subjects residing in urban Boston during the 2006–2007 and 2010–2011 seasons. Samples were generally collected between October and April of each winter season, which will be referred to by the latter year (2001 for 2000–2001).

Methods for sample collection and processing have been previously described in detail [6, 7, 9, 16]. In brief, we obtained nasopharyngeal swabs from children presenting to their primary care physician's office for well child care or an illness-related visit. Parents completed surveys describing the reason for the visit, acute illness symptoms, prior use of antibiotics, history of breastfeeding, number of children in the household, smoking in the household, daycare attendance, and other demographic variables (age, gender, child's race/ethnicity, household income). Information about dates and types of childhood vaccines received, presence of comorbidities, and recent antibiotic use were collected by medical record review.

7-Valent pneumococcal conjugate vaccine was available from 2000 to 2010, and children were considered "vaccinated" if they were up-to-date (UTD) by the following criteria: if they had received ≥ 1 dose if <6 months old; ≥ 2 doses if 6–11 months old; ≥ 3 doses if 12–15 months old; or ≥ 4 doses if 16 months old or older. Because PCV13 was not available in Massachusetts until April 2010, we considered children to be vaccinated with PCV13 in the 2011 season if they had received the following: ≥ 1 dose of PCV13 if <6 months old; ≥ 2 doses of PCV13 if 6–11 months old; ≥ 3 doses of any pneumococcal vaccine with at least 1 dose of PCV13 if 12–15 months old; or ≥ 4 doses of any pneumococcal vaccine with at least 1 dose of PCV13 if 16 months old or older [12]. This study was approved by the Harvard Pilgrim Health Care Institutional Review Board.

Laboratory Methods

Nasopharyngeal swabs were plated within 24 hours on selective media with gentamicin for identification of *S pneumoniae*. Serotype was determined using the Quellung reaction to antisera to specific capsular antigens (Serum Statens Institute, Copenhagen, Denmark). Pneumococcal isolates were identified as PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F), PCV13 additional serotypes (1, 3, 5, 6A, 7F, 19A), and non-PCV13 serotypes. Sequence types (STs) were determined through multilocus sequence typing [17, 18]. Antibiotic susceptibility testing was performed using E-tests for penicillin, ceftriaxone, erythromycin, clindamycin, trimethoprim-sulfamethoxazole, levofloxacin, and vancomycin. Pneumococci were classified as susceptible, intermediate, or resistant based on current Clinical and Laboratory Standards Institute (CLSI) breakpoints for nonmeningeal isolates [19, 20]. Penicillin nonsusceptible *S pneumoniae* was defined as any intermediate (4.0 mg/L) or resistant (≥ 8.0 mg/L) isolate. Ceftriaxone (2.0 mg/L, ≥ 4.0 mg/L), erythromycin (0.5 mg/L, >1.0 mg/L), and clindamycin (1.0–2.0 mg/L, >4.0 mg/L) nonsusceptibility were also defined as any intermediate or resistant isolate.

Data Analysis

We describe the prevalence of children colonized with PCV7 serotypes, additional PCV13 serotypes, and non-PCV13 serotypes in 2001, 2004, 2007, 2009, and 2011. The proportion of antibiotic-resistant isolates among all pneumococci isolated is presented, along with serotypes responsible for antibiotic resistance in 2011. Linear trends in colonization overall and by vaccine serotype were assessed using generalized linear mixed models using logistic regression with adjustment for clustering (nonindependence) of subjects within communities. We also assessed linear trend excluding 2001 when visual analysis suggested

an effect of the introduction of PCV7, and we assessed whether the 2011 prevalence of PCV13 serotypes deviated from the trend established from 2001 through 2009. We replicated these results in the subset of 8 communities included in all collection periods. When we compared our findings for all enrolled subjects to those in the 8 communities that were included in all collection periods, our findings were similar. Therefore, we present data based on isolates collected in all Massachusetts communities studied from 2001 through 2011.

We evaluated the impact of vaccination with PCV13 on overall carriage and PCV13 serotype carriage among children enrolled in 2007, 2009, and 2011 in the same 8 communities, when carriage with PCV7 serotypes were at its lowest. We used generalized linear mixed models to compare children who were vaccinated with PCV13 in 2011 versus children who were not vaccinated with PCV13 (ie, not UTD for PCV13 in 2011 or children swabbed before the availability of PCV13 in 2007 and 2009), accounting for clustering by community. Because younger children were more likely to receive PCV13 in the 2011 collection period, we present our analyses stratified by age group (6 to <24 months vs 2 to <7 years). Models were adjusted for gender, race or ethnicity, number of siblings ≤ 6 years old in the household, and childcare attendance. In addition, we explored the impact of recent antibiotic use and concurrent respiratory tract infection at time of swabbing, as determined by chart review, which were previously identified as factors associated with pneumococcal colonization [6, 7, 21, 22]. We tested for effect modification using interaction terms for concurrent respiratory tract infection and PCV13 vaccination status in our adjusted models, and we provide effect estimates as appropriate. In the absence of effect modification, the most parsimonious model was used in our final analyses. All analyses were performed using SAS software version 9.2 (SAS Institute, Cary, NC).

RESULTS

Study Population

We conducted surveillance in Massachusetts communities for pneumococcal colonization among children <7 years of age in 2001 ($n = 678$), 2004 ($n = 987$), 2007 (1540), 2009 ($n = 1011$), and 2011 ($n = 1164$). Across these periods, there were differences in the enrolled patient characteristics and their exposures (Table 1). Most notably, the proportion of children attending group childcare and who were breastfed increased over time, whereas antibiotic use in the past 8 weeks decreased in recent study periods.

In 2011, vaccination with any pneumococcal conjugate vaccine (ie, PCV7 or PCV13) exceeded 90% in all age groups (Figure 1). Because PCV13 was not available until

April 2010 in Massachusetts, younger children (who are seen more frequently for well child care) were more likely to have received PCV13, particularly those <24 months old. A smaller proportion of children 2 to <5 years of age (41%) had received a PCV13 catch-up booster, and very few children 5 to <7 years of age (2%) received PCV13, consistent with the timing of availability of PCV13 and with national recommendations for use in this age group.

Pneumococcal Colonization by Vaccine Serotype

Overall pneumococcal colonization declined between 2001 and 2004 and increased thereafter to the current level of 31% (Figure 2A). Between 2004 and 2011, the prevalence of pneumococcal colonization increased significantly (odds ratio [OR] per year, 1.05; 95% confidence interval [CI], 1.03, 1.08; $P < .0001$). In contrast to overall colonization, PCV7 serotype colonization declined significantly (OR per year, 0.74; 95% CI, 0.70, 0.79; $P < .0001$). There were no significant trends seen for 6 additional PCV13 serotypes before 2011 (OR per year, 1.03; 95% CI, 0.98, 1.08; $P = .26$). However, in the highly vaccinated age group of children 6 to <24 months old (Figure 2B), the odds of colonization with PCV13 serotypes decreased significantly in 2011 from the course suggested by the previous years (OR, 0.54; 95% CI, 0.30, 0.96; $P = .037$). In contrast, there were no significant declines noted for children 2 to <7 years of age in 2011. We did observe significant increases in non-PCV13 serotypes between 2001 and 2011 for all children (OR per year, 1.12; 95% CI, 1.10, 1.15; $P < .0001$); our findings for colonization with non-PCV13 serotypes were similar for both younger (OR per year, 1.15; 95% CI, 1.10, 1.19) and older children (OR per year, 1.10; 95% CI, 1.06, 1.13).

When individual serotypes were considered, the proportion of children colonized with 15B/C and 21 increased over the past decade. 15 B/C emerged as the most common serotype in 2011 (Figure 3). Among serotypes included in PCV13, 19A remained the second most common isolate in 2011, although its prevalence had declined from 2009. Small declines were also noted for serotype 6A and 7F, but not for serotype 3, in 2011.

Pneumococcal Colonization by Antibiotic Susceptibility

Erythromycin nonsusceptibility was most commonly identified, occurring in approximately one-quarter of pneumococcal isolates, followed by clindamycin and ceftriaxone nonsusceptibility (Figure 4). Less common were penicillin-intermediate ($\sim 5\%$) and penicillin-resistant ($\sim 2\%$) isolates, based on 2008 CLSI definitions for penicillin nonsusceptibility for nonmeningeal infections, although penicillin resistance increased significantly between 2001 and 2011 ($P = .001$).

Table 1. Characteristics of Children Swabbed in Massachusetts Communities, 2001–2011^a

	2001 (n = 678)	2004 (n = 987)	2007 (n = 1540)	2009 (n = 1011)	2011 (n = 1164)	P Value ^b
Age group						
<6 months	8.70%	4.96%	9.35%	7.72%	7.30%	<.001
6 to <12 months	16.52%	12.16%	17.27%	17.31%	18.13%	
12 to <24 months	21.24%	23.10%	25.65%	23.44%	23.20%	
2 to <5 yrs	36.14%	41.84%	34.81%	37.88%	35.14%	
5 to <7 yrs	17.40%	17.93%	12.92%	13.65%	16.24%	
Female gender	45.79%	52.79%	48.12%	48.17%	46.48%	.025
Young siblings (≤ 6 years) in household						
0	52.97%	50.47%	58.06%	53.75%	53.41%	.72
1	37.34%	39.02%	34.05%	36.84%	36.73%	
≥2	9.69%	10.51%	7.89%	9.41%	9.85%	
Group childcare attendance						
None or <4 hours/weeks	55.52%	48.59%	50.17%	43.44%	45.56%	<.001
4–10 hours/week	14.83%	11.53%	8.44%	12.28%	11.61%	
11–20 hours/week	5.77%	13.88%	8.37%	11.75%	10.11%	
>20 hours/week	23.89%	26.00%	33.02%	32.53%	32.72%	
Recent antibiotic use (chart only)						
<2 weeks	10.18%	10.33%	4.61%	7.72%	5.41%	<.001
2 to <4 weeks	8.26%	8.81%	6.88%	6.92%	6.62%	
4 to <6 weeks	7.37%	5.57%	4.55%	3.36%	3.44%	
6 to <8 weeks	6.19%	4.15%	5.45%	3.17%	2.84%	
≥8 weeks or none recorded	67.99%	71.12%	78.51%	78.83%	81.70%	
RTI at the time of specimen collection (chart only)	28.83%	27.14%	46.04%	39.27%	33.16%	<.001
Cigarette smoke exposure in household	29.73%	20.57%	19.83%	25.74%	22.17%	<.001
Breastfed						
No	38.55%	34.93%	27.38%	29.38%	23.91%	<.001
Yes, for <3 months	18.48%	16.89%	19.21%	20.27%	20.33%	
Yes, for 3–6 months	24.01%	21.46%	23.83%	22.11%	26.00%	
Yes, for >6 months	18.96%	26.71%	29.59%	28.25%	29.76%	
Race/ethnicity						
White non-Hispanic	77.83%	84.07%	53.19%	82.27%	69.41%	<.001
Black non-Hispanic	6.67%	3.86%	27.98%	5.15%	12.01%	
Hispanic/Latino	7.60%	5.50%	12.44%	7.42%	10.60%	
Asian/Pacific Islander	3.10%	1.99%	2.22%	4.02%	5.00%	
Other	4.81%	4.57%	4.17%	1.13%	2.98%	
Overall pneumococcal colonization	27.43%	23.30%	27.60%	28.68%	31.36%	.001
Pneumococcal colonization by serotype						
PCV7 serotypes	7.96%	3.44%	1.30%	0.59%	0.60%	<.001
Additional PCV13 serotypes	5.16%	5.07%	6.49%	5.74%	4.81%	.33
Non-PCV13 serotypes	9.14%	14.08%	19.81%	22.35%	25.95%	<.001
Serotype data missing	5.16%	0.71%	0.00%	0.00%	0.00%	–

Abbreviations: RTI, respiratory tract infection.

^aChildren enrolled from 16 Massachusetts communities in 2001 and 2004, 9 communities in 2007, 8 communities in 2009, and 9 communities in 2011.

^bUsing generalized linear mixed models to account for clustering by community to evaluate differences across swabbing seasons.

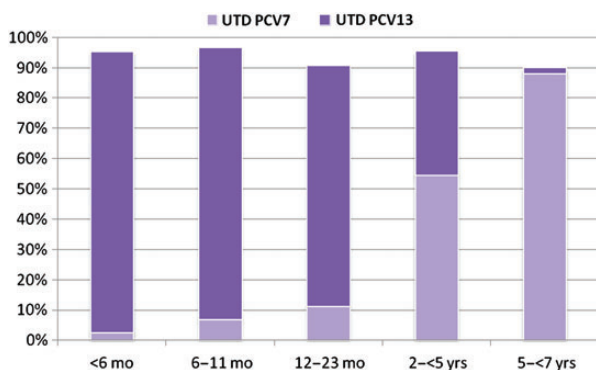


Figure 1. Proportion of children up-to-date (UTD) for PCV13 or PCV7 by age group in 2011.

Among nonsusceptible isolates in 2011, serotype 19A was responsible for 94% (17 of 18) of penicillin-intermediate, 100% (6 of 6) of penicillin-resistant, 68%

(25 of 37) of ceftriaxone nonsusceptible, 29% (29 of 101) of erythromycin nonsusceptible, and 39% (15 of 38) of clindamycin nonsusceptible isolates in 2011. Although serotype 19A declined in prevalence between 2009 and 2011, we did not note any parallel declines in the proportion of nonsusceptible isolates. Notably, ST320 increased as a proportion of 19A isolates over the past decade (0% in 2001, 4% in 2004, 15% in 2007, 45% in 2009, 46% in 2011), whereas ST199 has continued to decline (78% in 2001, 50% in 2004, 35% in 2007, 12% in 2009, 7% in 2011) (Figure 5), which has also been demonstrated in our previously published work [15].

Serotype 35B accounted for 27% (10 of 37) ceftriaxone nonsusceptible and 3% (3 of 101) of erythromycin nonsusceptible isolates. Serotypes 15A and 15B/C accounted for 12% (12 of 101) and 26% (26 of 101) of erythromycin

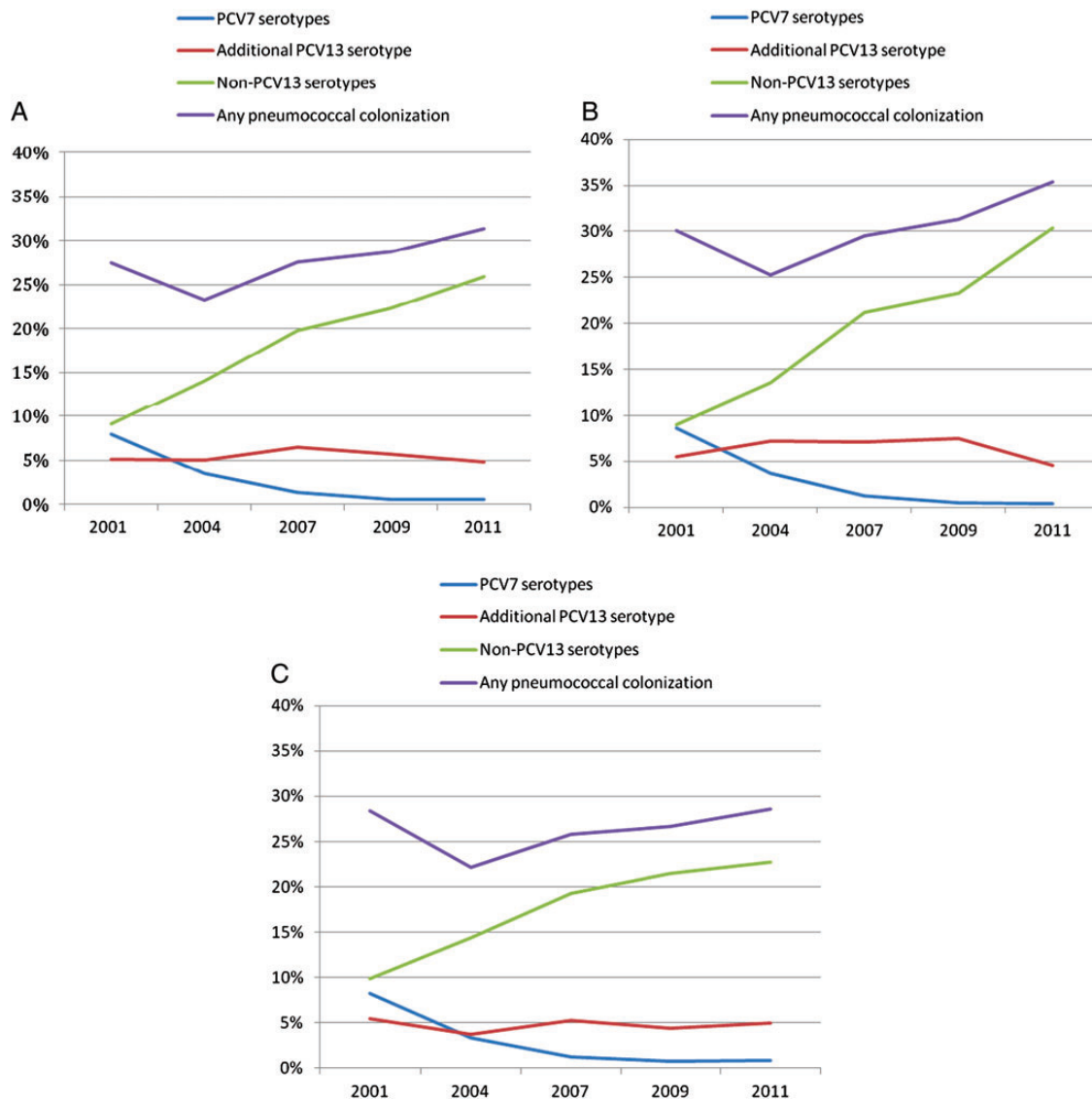


Figure 2. Pneumococcal colonization by vaccine serotype among (A) all swabbed children, (B) children 6–23 months, and (C) children 2 to <7 years of age, 2001–2011.

nonsusceptible isolates and 32% (12 of 38) and 8% (3 of 38) of clindamycin nonsusceptible isolates, respectively. Serotype 21 was responsible for only 1% (1 of 101) of erythromycin and 3% (1 of 38) of clindamycin nonsusceptible isolates. Serotype 3 also accounted for very little antibiotic resistance (2% erythromycin; 3% clindamycin) in the 2011 sample.

Impact of PCV13 on Pneumococcal Colonization

Overall colonization rates in children 6–23 months (Table 2A) or 2 to <7 years (Table 2B) of age who were vaccinated with PCV13 in 2011 were comparable to children who did not receive PCV13 in 2007, 2009, and 2011, adjusted for known risk factors for colonization. Probability of colonization with a PCV13 serotype revealed a different relationship. Among 6- to 23-month-old children without a concomitant respiratory tract infection,

the prevalence of colonization with PCV13 serotypes was significantly lower among children who were vaccinated with PCV13 vaccine (adjusted OR, 0.30; 95% CI, 0.11, 0.78; $P = .014$) (Table 2A). This protective effect was not observed among children with a concomitant respiratory tract infection. Among 2- to <7-year-old children, we did not observe significant changes in the relative rate of overall pneumococcal colonization or colonization with PCV13 serotypes among PCV13-vaccinated children (Table 2B).

DISCUSSION

We evaluated the impact of PCV13 vaccination on rates of pneumococcal colonization during the 2010–2011 winter season in Massachusetts, where we have conducted surveillance since 2001. Even though introduction of PCV13 in April 2010 occurred shortly before our surveillance

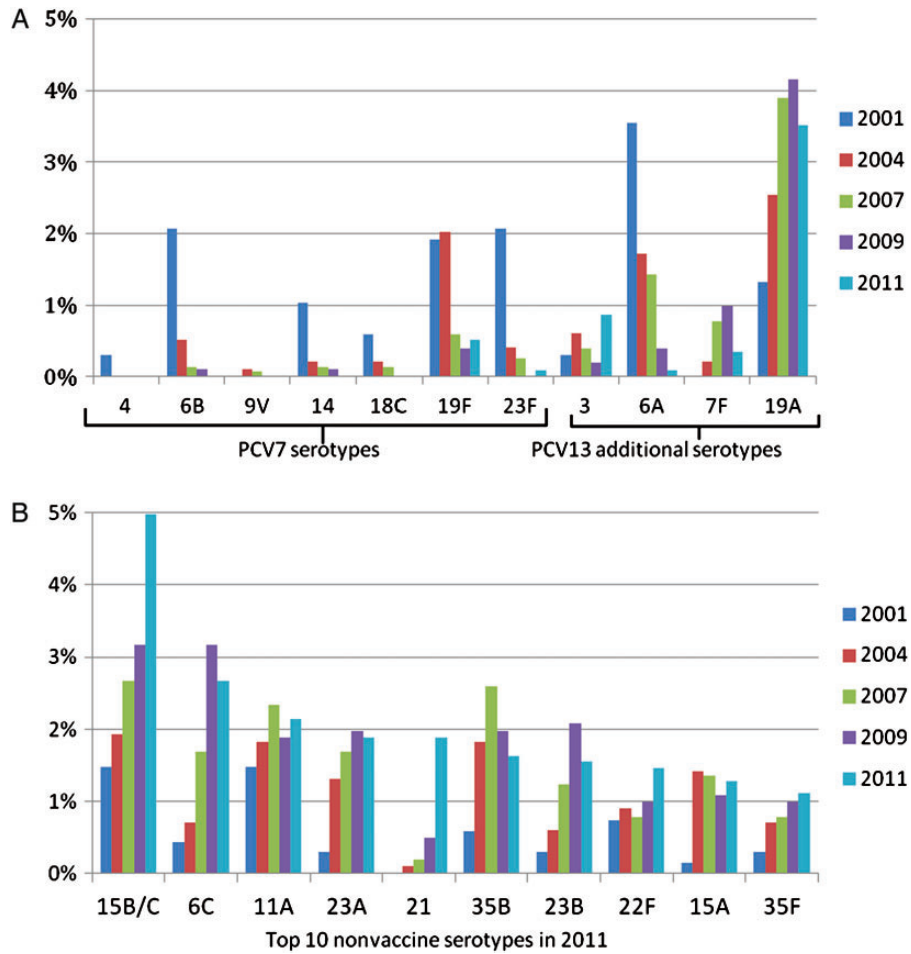


Figure 3. Pneumococcal colonization by (A) PCV7 and additional PCV13 serotypes, and (B) 10 most common non-PCV13 vaccine serotypes among Massachusetts children, 2001–2011.

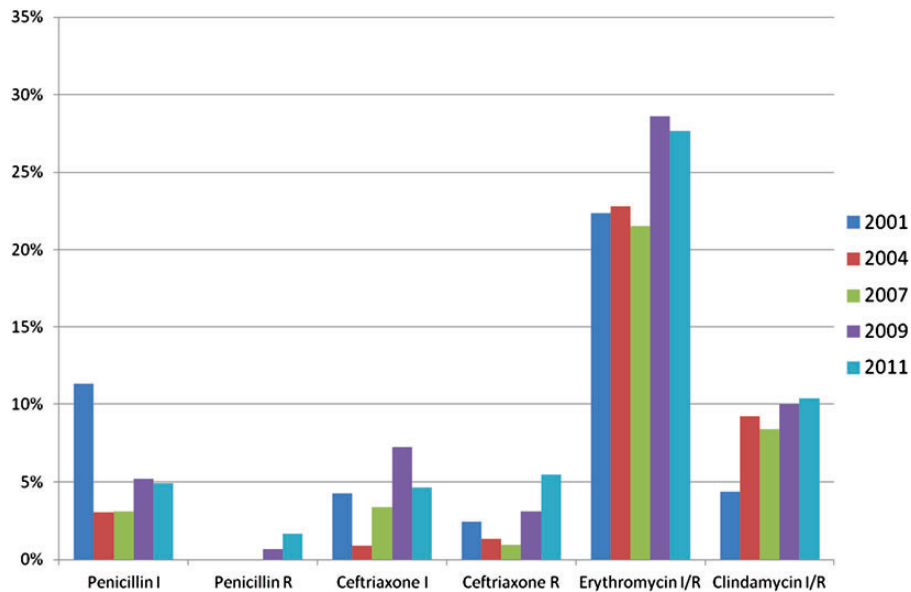


Figure 4. Proportion of antibiotic-resistant pneumococcal isolates, 2001–2011.

began, rates of colonization with PCV13 serotypes were notably lower in 2011 compared with prior surveillance periods in a highly vaccinated cohort of children 6–23 months of age. Similar declines were not noted in children 2 to <7 years of age, where vaccine uptake was much lower, consistent with the timing of vaccine introduction and recommendations for use in this age group. Nationally, only 27% of children 2 to <5 years of age were estimated to have received the recommended supplemental dose of PCV13 by 2011 [23]. With these lower vaccination rates among older children, we would not yet anticipate seeing

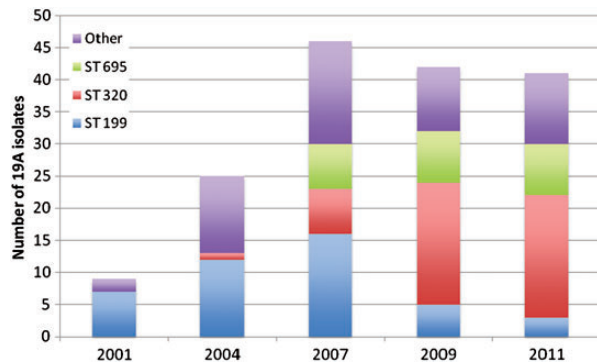


Figure 5. Frequency of 19A isolates identified as ST199, ST320, ST695, and other STs, 2001–2011.

the full benefit of both direct protection and herd effect from PCV13 vaccination [24–26].

We were surprised by the finding that the presence of a respiratory tract infection at the time of swabbing mitigated the impact of PCV13 vaccination on colonization with PCV13 serotypes in young children. It is generally accepted that the recovery of *S pneumoniae* from the nasopharynx is higher among children with respiratory tract infection, due to increased secretions recovered or a higher bacterial load within the nasopharynx [27]. Alternatively, one may speculate that the presence of a respiratory tract infection may facilitate coacquisition of *S pneumoniae* more generally, although we would not anticipate this to be limited to PCV13 serotypes [28]. Regardless, the vaccine appears to have had an overall beneficial effect in reducing carriage of PCV13 serotypes among young, healthy children. This result may be clinically significant because particular serotypes included in the vaccine, such as 19A, are a major cause of IPD in the post-PCV7 era.

In contrast, colonization with non-PCV13 serotypes appears to be increasing over the past decade, with 15B/C, 19A, 6C, and 11A identified as the most common isolates in 2011. Although serotype 6C is not currently included in the PCV13 vaccine, the inclusion of 6A, which has been reported to induce functional anti-6C opsonophagocytic

Table 2A. Multivariate Regression Model to Evaluate the Effects of PCV13 Vaccination on Overall Colonization and Colonization With PCV13 Serotypes. Results Are Presented for 6- to 23-Month-Old Children

	Any Pneumococcal Colonization		Colonization With PCV13 Serotypes ^a	
	OR (95% CI)	P Value ^b	OR (95% CI)	P Value ^b
6-23 month old children (n = 1209)				
RTI at the time of specimen collection	1.85 (1.42, 2.41)	<.001	–	–
Vaccinated with PCV13	1.07 (.81, 1.42)	.63	–	–
Vaccinated with PCV13 and presence of RTI	–	–	1.36 (.66, 2.77)	.40
Not vaccinated with PCV13 and presence of RTI	–	–	1.40 (.84, 2.34)	.20
Vaccinated with PCV13 and No RTI	–	–	0.30 (.11, 0.78)	.014
Not vaccinated with PCV13 and no RTI	–	–	1.0	–
Young siblings (≤6 years) in household		<.001		.005
0	1.0		1.0	
1	2.31 (1.75, 3.04)		1.15 (.70, 1.89)	
≥2	3.03 (2.00, 4.60)		3.01 (1.53, 5.92)	
Group childcare attendance		<.001		<.001
None or <4 hours/weeks	1.0		1.0	
4–20 hours/week	2.00 (1.33, 3.01)		1.61 (.76, 3.40)	
>20 hours/week	3.05 (2.23, 4.18)		3.04 (1.83, 5.06)	
Recent antibiotic use		<.001		.24
<2 weeks	0.29 (.17, 0.52)		0.82 (.33, 2.03)	
2 to <4 weeks	0.63 (.41, 0.97)		1.86 (.99, 3.50)	
4 to <8 weeks	0.61 (.39, 0.94)		1.04 (.51, 2.14)	
≥8 weeks or none recorded	1.0		1.0	

Abbreviations: CI, confidence interval; OR, odds ratio; RTI, respiratory tract infection.

^aP value for interaction term for vaccinated with PCV13 ^bpresence of RTI = 0.053.

^bType III test of fixed effects.

Table 2B. Multivariate Regression Model to Evaluate the Effects of PCV13 Vaccination on Overall Colonization and Colonization With PCV13 Serotypes. Results Are Presented for 2- to <7-Year-Old Children Swabbed in 2007, 2009, and 2011, Combined

	Any Pneumococcal Colonization		Colonization With PCV13 Serotypes	
	OR (95% CI)	P Value ^a	OR (95% CI)	P Value ^a
2- to <7-year-old children (n = 1462)				
Vaccinated with PCV13	1.23 (.85, 1.78)	.28	1.17 (.58, 2.34)	.66
Young siblings (≤6 years) in household		.80		.93
0	1.0		1.0	
1	0.98 (.77, 1.26)		1.01 (.63, 1.63)	
≥2	0.86 (.55, 1.34)		0.86 (.35, 2.08)	
Group childcare attendance		.001		.72
None or <4 hours/weeks	1.0		1.0	
4–20 hours/week	1.43 (1.03, 1.97)		1.12 (.61, 2.08)	
>20 hours/week	1.87 (1.36, 2.55)		1.28 (.70, 2.32)	
Recent antibiotic use		<.001		.56
<2 weeks	0.25 (.13, .50)		0.53 (.16, 1.75)	
2 to <4 weeks	0.38 (.22, .65)		0.78 (.30, 2.01)	
4 to <8 weeks	0.65 (.41, 1.03)		1.33 (.64, 2.79)	
≥8 weeks or none recorded	1.0		1.0	
RTI at time of specimen collection	1.18 (.93, 1.50)	.17	1.42 (.90, 2.24)	.13

Abbreviations: CI, confidence interval; OR, odds ratio; RTI, respiratory tract infection.

^aType III test of fixed effects.

responses, may reduce 6C colonization in the PCV13 era [29, 30]. Additional surveillance will be needed to understand whether the decrease in prevalence of 6C colonization we observed in 2011 is maintained. These changes likely reflect (1) the decline in new acquisitions of additional PCV13 serotypes as a result of vaccine-induced immunity and (2) expansion of less frequent genotypes with non-PCV13 serotypes.

We have not yet seen substantial changes in patterns of antibiotic nonsusceptibility in 2011, despite a modest decline in the carriage prevalence of 19A. These findings mirror observations in US data on IPD that describe a stable proportion of 19A isolates that are increasingly antimicrobial-resistant due to the dramatic expansion of multidrug-resistant ST320 and corresponding declines in ST199 [31]. Although it unclear why ST320 emerged as the predominant 19A clone, it is plausible that the key to its success was a combination of vaccination pressure and continued antimicrobial pressure. As widespread use of PCV13 adds to the selective pressure on isolates with a 19A capsule, further monitoring of the ongoing evolution of the genetic structure of pneumococcus is warranted.

This analysis is based on surveillance in the same communities over a decade, with collection of nasopharyngeal isolates as well as detailed information on epidemiologic risk factors. Although it appears that the association of certain risk factors with pneumococcal colonization has changed over time in these communities, such as group childcare attendance, recent antibiotic use, cigarette smoke exposure in household, and breastfeeding rates, PCV13 vaccination

remains an independent predictor of lower likelihood of colonization with PCV13 serotypes in Massachusetts children 6–23 months of age. These findings are similar to those found in children diagnosed with otitis media, in which 19A and 7F carriage rates were found to be lower in PCV13- versus PCV7-vaccinated patients [32].

Because we do not follow colonization patterns in the same individuals over time, we cannot comment about the duration of carriage for particular serotypes, nor can we directly calculate attack rates for invasive disease for specific serotypes. However, our population-based approach has allowed us to assess shifts in the circulating pneumococcal strains among young children in the same communities, over the period of introduction first of PCV7, and now PCV13. As such, it represents a model for understanding the response of a bacterial population to the significant selective pressure of vaccine introduction.

CONCLUSIONS

Our findings suggest that even within 1 year of implementation, PCV13 has had an impact on the circulating population of pneumococci among young children in our communities in Massachusetts. We anticipate further reductions in PCV13 serotypes as additional age cohorts are vaccinated over time, similar to our observations of the impact of PCV7. It is also likely, we believe, that serotype replacement and expansion of existing strains will continue to mitigate the overall impact of PCV13 vaccine on overall pneumococcal colonization.

Acknowledgments

We are grateful to Marc Lipsitch contributions to our study. We also thank Chelsea Nahill, Hilana Bernheimer, Nandini Vijayakumar, and Verna Moran for their dedication to this project, and we extend our appreciation to the following participating practices: Alan Bulotsky MD & Associates (Brockton, MA); Berkshire Pediatric Associates (Pittsfield, MA); Cape Ann Pediatricians (Gloucester, MA); Children's Health Care (Newburyport, MA); Harvard Vanguard Medical Associates (Chelmsford, MA); Medical Associates Pediatrics (Leominster, MA); Middleboro Pediatrics (Lakeville, MA); Needham Pediatrics (Needham, MA); and Boston Medical Center (Boston, MA). We also extend our gratitude to the many parents and children who made this study possible.

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Financial support. This work was supported by the National Institute of Allergy And Infectious Diseases of the National Institutes of Health under Award Number R01AI066304 (to J. A. F.).

Potential conflicts of interest. S. I. P. has been on Global Pneumococcal Vaccine Advisory Boards at Pfizer, GSKbio, and Merck.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

- Centers for Disease Control and Prevention (CDC). Invasive pneumococcal disease in young children before licensure of 13-valent pneumococcal conjugate vaccine - United States, 2007. *MMWR Morb Mortal Wkly Rep* 2010; 59:253-7.
- O'Brien KL, Millar EV, Zell ER, et al. Effect of pneumococcal conjugate vaccine on nasopharyngeal colonization among immunized and unimmunized children in a community-randomized trial. *J Infect Dis* 2007; 196:1211-20.
- Pelton SI, Huot H, Finkelstein JA, et al. Emergence of 19A as virulent and multidrug resistant *Pneumococcus* in Massachusetts following universal immunization of infants with pneumococcal conjugate vaccine. *Pediatr Infect Dis J* 2007; 26:468-72.
- Sharma D, Baughman W, Holst A, et al. Pneumococcal carriage and invasive disease in children before introduction of the 13-valent conjugate vaccine: comparison with the pre-7-valent conjugate vaccine era. *Pediatr Infect Dis J* 2013; 32:e45-53.
- Weatherholtz R, Millar EV, Moulton LH, et al. Invasive pneumococcal disease a decade after pneumococcal conjugate vaccine use in an American Indian population at high risk for disease. *Clin Infect Dis* 2010; 50:1238-46.
- Wroe PC, Lee GM, Finkelstein JA, et al. Pneumococcal carriage and antibiotic resistance in young children before 13-valent conjugate vaccine. *Pediatr Infect Dis J* 2012; 31:249-54.
- Huang SS, Hinrichsen VL, Stevenson AE, et al. Continued impact of pneumococcal conjugate vaccine on carriage in young children. *Pediatrics* 2009; 124:e1-11.
- Centers for Disease Control and Prevention (CDC). Pneumonia hospitalizations among young children before and after introduction of pneumococcal conjugate vaccine—United States, 1997–2006. *MMWR Morb Mortal Wkly Rep* 2009; v58:1-4.
- Huang SS, Platt R, Rifas-Shiman SL, et al., Post-PCV 7 changes in colonizing pneumococcal serotypes in 16 Massachusetts communities, 2001, 2004. *Pediatrics* 2005; 116:e408-13.
- Wroe PC, Lee GM, Finkelstein JA, et al. Pneumococcal carriage and antibiotic resistance in young children before 13-valent conjugate vaccine. *Pediatr Infect Dis J* 2012; 31:249-54.
- Centers for Disease Control and Prevention (CDC). Licensure of a 13-valent pneumococcal conjugate vaccine (PCV13) and recommendations for use among children - Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Morb Mortal Wkly Rep* 2010; v59:258-61.
- American Academy of Pediatrics Committee on Infectious Diseases. Recommendations for the prevention of *Streptococcus pneumoniae* infections in infants and children: use of 13-valent pneumococcal conjugate vaccine (PCV13) and pneumococcal polysaccharide vaccine (PPSV23). *Pediatrics* 2010; 126:186-90.
- Rubin JL, McGarry LJ, Strutton DR, et al. Public health and economic impact of the 13-valent pneumococcal conjugate vaccine (PCV13) in the United States. *Vaccine* 2010; 28:7634-43.
- Pelton SI, Huot H, Finkelstein JA, et al. Emergence of 19A as virulent and multidrug resistant *Pneumococcus* in Massachusetts following universal immunization of infants with pneumococcal conjugate vaccine. *Pediatr Infect Dis J* 2007; 26:468-72.
- Hanage WP, Bishop CJ, Lee GM, et al. Clonal replacement among 19A *Streptococcus pneumoniae* in Massachusetts, prior to 13 valent conjugate vaccination. *Vaccine* 2011; 29:8877-81.
- Finkelstein JA, Huang SS, Daniel J, et al. Antibiotic-resistant *Streptococcus pneumoniae* in the heptavalent pneumococcal conjugate vaccine era: predictors of carriage in a multicommunity sample. *Pediatrics* 2003; 112:862-9.
- Hanage WP, Kaijalainen T, Herva E, et al. Using multilocus sequence data to define the pneumococcus. *J Bacteriol* 2005; 187: 6223-30.
- Enright MC, Spratt BG. A multilocus sequence typing scheme for *Streptococcus pneumoniae*: identification of clones associated with serious invasive disease. *Microbiology* 1998; 144(Pt 11):3049-60.
- Institute CaLS. Performance Standards for Antimicrobial Susceptibility Testing; Sixteenth Informational Supplement. Vol. M100-S16: CLSI, Wayne, PA; 2004; pp 126-8.
- Institute CaLS. Performance Standards for Antimicrobial Susceptibility Testing; Seventeenth Informational Supplement. Vol. M100-S16: CLSI, Wayne, PA; 2007; pp 126-8.
- Abdullahi O, Karani A, Tigoi CC, et al. The prevalence and risk factors for pneumococcal colonization of the nasopharynx among children in Kilifi District, Kenya. *PLoS One* 2012; 7: e30787.
- Pebody RG, Morgan O, Choi Y, et al. Use of antibiotics and risk factors for carriage of *Streptococcus pneumoniae*: a longitudinal household study in the United Kingdom. *Epidemiol Infect* 2009; 137:555-61.
- Centers for Disease Control and Prevention (CDC). Invasive pneumococcal disease and 13-valent pneumococcal conjugate vaccine (PCV13) coverage among children aged <=59 months—selected U.S. regions, 2010–2011. *MMWR Morb Mortal Wkly Rep* 2011; 60:1477-81.
- Hammit LL, Bruden DL, Butler JC, et al. Indirect effect of conjugate vaccine on adult carriage of *Streptococcus pneumoniae*: an explanation of trends in invasive pneumococcal disease. *J Infect Dis* 2006; 193:1487-94.
- Centers for Disease Control and Prevention (CDC). Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease—United States, 1998–2003. *MMWR Morb Mortal Wkly Rep* 2005; 54:893-7.
- Miller E, Andrews NJ, Waight PA, et al. Herd immunity and serotype replacement 4 years after seven-valent pneumococcal conjugate vaccination in England and Wales: an observational cohort study. *Lancet Infect Dis* 2011; 11:760-8.

27. Short KR, Diavatopoulos DA, Thornton R, et al. Influenza virus induces bacterial and nonbacterial otitis media. *J Infect Dis* 2011; 204:1857–65.
28. Gwaltney JM Jr, Sande MA, Austrian R, Hendley JO. Spread of *Streptococcus pneumoniae* in families. II. Relation of transfer of *S. pneumoniae* to incidence of colds and serum antibody. *J Infect Dis* 1975; 132:62–8.
29. Cooper D, Yu X, Sidhu M, et al. The 13-valent pneumococcal conjugate vaccine (PCV13) elicits cross-functional opsonophagocytic killing responses in humans to *Streptococcus pneumoniae* serotypes 6C and 7A. *Vaccine* 2011; 29: 7207–11.
30. Ho PL, Ang I, Chow KH, et al. The prevalence and characteristics of *Streptococcus pneumoniae* isolates expressing serotypes 6C and 6D in Hong Kong prior to the introduction of the 7-valent pneumococcal conjugate vaccine. *Diagn Microbiol Infect Dis* 2010; 68:439–44.
31. Beall BW, Gertz RE, Hulkower RL, et al. Shifting genetic structure of invasive serotype 19A pneumococci in the United States. *J Infect Dis* 2011; 203:1360–8.
32. Cohen R, Levy C, Bingen E, et al. Impact of 13-valent pneumococcal conjugate vaccine on pneumococcal nasopharyngeal carriage in children with acute otitis media. *Pediatr Infect Dis J* 2012; 31:297–301.